PATENT

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Name of Person Mailing Paper or Fee

Therese Duignan
Signature of Person Mailing Paper or Fee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

06/358055

U.S. Patent No: 4,490,351

For: **METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS**

Issued: December 25, 1984

Inventor: Leland C. Clark, Jr.

Box PATENT EXT.
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

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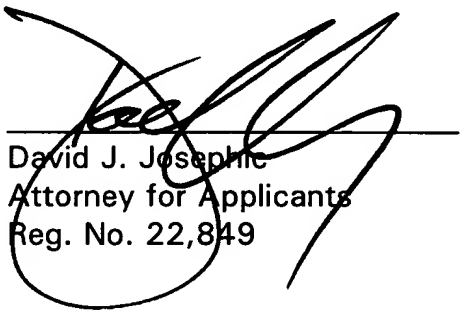
TRANSMITTAL LETTER

Submitted herewith is an Application and a true copy thereof for an Extension of Patent Term under 35 U.S.C. §156 for the above-identified patent.

Also enclosed is our check made out to the Commissioner of Patents

and Trademarks in the amount of $1,120.00 as payment for the application fee. The Commissioner is hereby authorized to charge to our deposit account, No. 23-3000, any additional fees due in connection with this application. If there are any questions concerning this application, please telephone the undersigned.

Respectfully submitted,



Dated: November 25, 1997

David J. Josephic
Attorney for Applicants
Reg. No. 22,849

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No: 4,490,351

For: **METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS**

Issued: December 25, 1984

Inventor: Leland C. Clark, Jr.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION PURSUANT TO 37 C.F.R. §1.740(b)

I, David J. Josephic, hereby depose and say:

(1) I am a registered patent attorney authorized to practice before the Patent and Trademark Office and having general authority from the owner of to act on its behalf in patent matters as related to an application to extend the term of the captioned patent to which this Declaration is attached (hereinafter "the application");

(2) I have reviewed and understand the contents of the application submitted herewith pursuant to 37 C.F.R. §1.740;

(3) I believe the patent is subject to extension pursuant to 37 C.F.R. §1.710;

(4) I believe that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

(5) I believe the patent for which the extension is being sought meets the conditions for extension of term of a patent set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, the patent or any extension of the patent term issuing as a result of the application.

Respectfully submitted,

Dated:

David J. Josephic
Attorney for Applicants
Reg. No. 22,849

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No: 4,490,351
For: **METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS**
Issued: December 25, 1984
Inventor: Leland C. Clark, Jr.
Attn'y Docket: VTRO-28

Cincinnati, OH 45202 November 25, 1997

BOX PATENT EXT.
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM
OF U.S. PATENT NO. 4,490,351 UNDER 35 U.S.C. §156

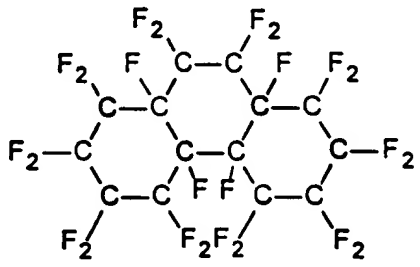
Vitrophage, Inc., the assignee of U.S. Patent No. 4,490,351, and FDA Applicant and owner of all regulatory review data on which this application is based, hereby requests that the term of U.S. Patent No. 4,490,351 be extended to expire on March 15, 2007. Ownership documents of Vitrophage, Inc., including filing as of this date a recordation in the U.S. Patent and Trademark Office, are attached as Exhibit (A).

The numbering of the following paragraphs corresponds to the numbering of the requirements for a formal application under 35 U.S.C. §156 as set forth in 37 C.F.R. §1.740, effective March 24, 1987, as amended on July 20, 1989 and December 13, 1991.

1. The approved device for the approved indication, to be marketed under the tradename VITREON®, is a sterile intraocular fluid of purified perfluorocarbon liquid. The bulk of the perfluorocarbon liquid is perfluorophenanthrene, otherwise known as perfluoroperhydrophenanthrene or perfluorotetradecahydrophenanthrene and hereinafter referred to as perfluorophenanthrene. Perfluoro-n-butyldecalin and related perfluorinated isomers are present in minor amounts.

Perfluorophenanthrene is the active ingredient contained in the approved device.

The chemical structure of perfluorophenanthrene is represented by the formula $C_{14}F_{24}$ and the following structure:



The approved device has the following physical properties: it is optically clear, it is immiscible with water, and it is easily injectable.

The approved device has the following chemical properties: a molecular weight of 624.12, a specific gravity of 2.03, a surface tension of 23.9 dynes/cm at 25°C, a refractive index of 1.3340, a vapor pressure of 0.35 torr at 37°C, a viscosity of 7.80 centistoke at 25°C, and a boiling point of 215°C.

The complete composition is more fully described in the package insert which is attached hereto as Exhibit (B).

2. Regulatory review of the approved device for the approved indication occurred under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§321 et seq., the applicable provision being 21 U.S.C. §360(e), also known as Section 515 of the Federal Food, Drug, and Cosmetic Act.

3. The date on which the device received permission for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act is September 30, 1997 as evidenced by the FDA Product Approval Letter, a copy of which is attached hereto as Exhibit (C).

4. §1.740(a)(4) is not applicable to medical devices.

5. This application is being submitted within the 60 day period permitted for submission, pursuant to 37 C.F.R. §1.720(f). The last day on which this application can be submitted is November 29, 1997.

6. A complete identification of the patent for which extension is being sought is as follows:

Inventor:	Leland C. Clark, Jr.
U.S. Patent No.:	4,490,351
Title:	Methods of Treating Disorders of an Eye with Liquid Perfluorocarbons
Issue Date:	December 25, 1984
Expiration Date:	March 15, 2002

7. A copy of U.S. Patent No. 4,490,351 is attached hereto as Exhibit (D).

8. No Terminal Disclaimer, Certificate of Correction, or Reexamination Certificate has issued in the patent. Copies of the Receipts of Maintenance Fee Payments are attached hereto as Exhibit (E).

9. The claims of U.S. Patent No. 4,490,351 ('351 patent) encompass the approved device for use as a surgical aid in treating patients with retinal detachments as described in detail below.

The interpretation and construction of patent claims, which define the scope of the patentee's rights under the patent, is a matter of law exclusively for the court. *Markman v. Westview Instruments, Inc.*, 34 USPQ2d 1321 (Fed. Cir. 1995), *en banc*, aff'd 38 USPQ2d 1461 (1996). Moreover, the plain language of the claims, the specification and the prosecution history in the PTO are the principal bases upon which that legal resolution is to be made. *Vitronics Corp. v. Conceptronics, Inc.*, 39 USPQ2d 1573 (Fed. Cir. 1996).

The approved device is a perfluorophenanthrene, otherwise known as perfluoroperhydrophenanthrene or perfluorotetradecahydrophenanthrene (column 6, lines 1-2 of the '351 patent specification) intraocular liquid. As stated at column 4, lines 11-13 and lines 59-68 to column 5, lines 1-2:

> This invention is directed to the use of perfluorocarbon liquids and substituted derivatives thereof in ophthalmological disorders....Furthermore, these dense

> compounds, having specific gravities greater than one, can be ideally employed in the treatment of retinal tears or detachments. For instance, currently a physician, during surgery or treatment of a patient during retinal detachment, will lie on his back and the patient is lying on his posterior surface. In contrast, the use of liquids of this invention during such treatment enables the detached retina to be mechanically supported against the choroid while the patient rests on his back and the physician stands or sits in a normal position. The novel liquids may simply be removed after the retina is attached, if desired.

The approved device is indicated for use as an intraoperative surgical aid during vitreoretinal surgery in patients with primary and recurrent complicated retinal detachments. Complicated cases include giant retinal tear or retinal dialysis, proliferative vitreoretinopathy, proliferative diabetic retinopathy, tractional retinal detachments, and blunt or penetrating ocular trauma.

Claim 1 encompasses the approved device for the approved indication because it covers a method of treating an intraocular structural disorder by introducing into the intraocular structure under treatment a liquid comprising a liquid perfluorocarbon or substituted derivative thereof in an effective amount. The approved device is perfluorophenanthrene intraocular liquid which is a liquid perfluorocarbon within the literal scope of claim 1. Furthermore, claim 1 literally covers the use of the device in treating an intraocular structural disorder (i.e., complicated retinal detachment) by introducing the device into the intraocular structure in an effective amount.

Claims 2-4 encompass the approved device for the approved indication because each is directed to a method of introducing the liquid perfluorocarbon,

which includes the approved device for the approved indication, into the vitreous of the eye and substantially replacing the vitreous with the approved device for the approved indication which may be done by withdrawing vitreous from the eye and simultaneously introducing the approved device for the approved indication into the vitreous.

Claim 5 encompasses the approved device for the approved indication because it is directed to replacing the aqueous with the liquid perfluorocarbon, which includes the approved device for the approved indication.

Claim 11 encompasses the approved device for the approved indication because it is directed to the use of a liquid perfluorocarbon which is a neat liquid, which includes the approved device for the approved indication.

Claim 12 encompasses the approved device for the approved indication because it is directed to a liquid perfluorocarbon which is a perfluorocyclocarbon, which includes the approved device.

Claim 17 encompasses the approved device for the approved indication because it is directed to the use of a liquid perfluorocarbon, which includes the approved device, to repair a retinal disorder by introducing the liquid perfluorocarbon into the vitreous and positioning an animal (i.e., a human patient) so that the device maintains the retina against the choroid of the eye to repair the retina, and maintaining the animal in the position for a sufficient time to effect the repair.

Claim 18 encompasses the approved device for the approved indication because it is directed to the use of the liquid perfluorocarbon of claim 17, which includes the approved device, to repair a detached or a torn retina.

Claim 19 encompass the approved device for the approved indication because it is directed to removing the liquid perfluorocarbon of claim 17, which includes the approved device, from the vitreous after the repair.

Claim 23 encompasses the approved device for the approved indication because it is directed to the use of a substantially transparent liquid perfluorocarbon, which includes the approved device, to treat an intraocular structural disorder by introducing the substantially transparent liquid perfluorocarbon in an effective amount to treat the disorder.

Claim 24 encompasses the approved device for the approved indication because it is directed to the perfluorocarbon of claim 23 which is a perfluorocyclocarbon, which includes the approved device.

Claim 26 encompasses the approved device for the approved indication because it is directed to the use of a liquid perfluorocarbon, which includes the approved device for the approved indication, to treat an intraocular structural disorder by introducing the perfluorocarbon in an effective amount into a structure of the eye under treatment (e.g., the anterior chamber, the posterior chamber, and vitreous body).

10. This is a statement providing the relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for the captioned patent.

The claims of U.S. Patent No. 4,490,351 cover a drug or a medical device. VITREON® was initially considered to be a drug rather than a medical device. On October 11, 1989, Dr. Gholam A. Peyman submitted to FDA's Center for Drug Evaluation and Research (CDER) an Investigational New Drug application (IND) for a Phase I clinical investigation of "perfluorophenanthrene as a temporary vitreous substitute" in humans. This submission was assigned IND No. 33,858. On April 13, 1990, Dr. Peyman received a letter from Robert L. Sheridan, Director, Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), announcing that FDA had determined that

> liquid fluorocarbon, when used for intraocular injection, is a medical device and has, therefore, transferred regulatory control of this device to [CDRH]. Although you were approved to conduct a Phase I investigation under the [IND] regulation, your investigation must now be conducted in accordance with the [IDE regulations]. For purposes of recordkeeping, the IDE number G900050 has been assigned to your investigation.

The letter acknowledged that "[Dr. Peyman has] already completed the first phase of [the] investigation (i.e., 15 subjects)." A copy of FDA's letter is included as Exhibit (F).

The effective date of the Investigational Device Exemption (IDE) and the IDE number are as follows:

Effective date of the IDE:	November 10, 1989
IDE Number:	G900050

11. The following is a brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved device for the approved indication, and the significant dates applicable to such activities.

Chronology of Major Communications Between Applicant and FDA from October 11, 1989 to July 29, 1997

Re: IDE No. G900050

Date	Subject
October 11, 1989 -	Letter from Dr. Gholam A. Peyman to Paul Chapman, Central Document Room, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), submitting an original Investigational New Drug Application (IND) for a Phase I clinical investigation of "perfluorophenanthrene as a temporary vitreous substitute" in humans. The request is limited to a study of 15 patients.
March 20, 1990 -	Letter from Dr. Gholam A. Peyman to CDER, FDA, proposing to expand the clinical investigation (designated as IND No. 33,858) to a Phase II clinical investigation in humans.
April 13, 1990 -	Letter from Robert L. Sheridan, Director, Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), to Dr. Gholam A. Peyman, announcing that "liquid fluorocarbon, when used for intraocular injection," has been determined to be a medical device and that jurisdiction over the product has been transferred from CDER to CDRH. "For purposes of recordkeeping," the application is assigned Investigational Device Exemption (IDE) No. G900050. Expansion of the study to Phase II is conditionally approved. The letter acknowledges that "[Dr. Peyman has] already completed the first phase of [the] investigation (i.e., 15 subjects)."

June 8, 1990 - Letter from Robert L. Sheridan, Director, ODE, to Dr. Gholam A. Peyman, announcing that the deficiencies identified in the conditional approval letter have been resolved and that the study may move forward with Phase II.

December 21, 1990 - Letter from Dr. Gholam A. Peyman to ODE, summarizing Phases I and II of the clinical investigation under IDE No. G900050 and requesting permission to expand the study to Phase III.

January 23, 1991 - Letter from Dr. Richard Lippman, DOD - ODE, to Dr. Gholam A. Peyman, announcing approval of the expansion of the clinical investigation under IDE No. G900050 to Phase III (limited to 100 subjects and 10 institutions).

July 30, 1991 - Letter from Mark A. Sievers, Keller and Heckman, to Richard E. Lippman, DOD - ODE, providing Dr. Peyman's Phase III report on the clinical testing being conducted under IDE No. G900050 and requesting permission to expand the study to include 10 new testing centers.

August 22, 1991 - Letter from Mark A. Sievers, Keller and Heckman, to Richard E. Lippman, DOD - ODE, modifying the request in the July 30, 1991 submission regarding expansion of the Phase III study under IDE No. G900050. Clarifies that Dr. Peyman proposed that the Phase III study be expanded to include 10 new testing centers and a maximum of 100 new subjects.

August 29, 1991 - Letter from Richard E. Lippman, DOD - ODE, to Mark A. Sievers, Keller and Heckman, announcing approval of the expansion to the Phase III study under IDE No. G900050. Investigation is limited to a total of 200 subjects and 20 institutions.

November 25, 1991 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH proposing expansion of the study to include an additional 400 subjects.

December 19, 1991 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH responding to a request from Carol Arras, DOD - ODE, to provide updated information on the investigators participating in the Phase III investigation conducted pursuant to IDE No. G900050.

January 3, 1991 - Letter from Richard E. Lippman, DOD - ODE, to Mark A. Sievers, Keller and Heckman, announcing approval of the November 25, 1991 supplement to the IDE application proposing expansion of the study to include an additional 400 subjects. The investigation is limited to 20 institutions and 600 total subjects.

March 31, 1992 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH to supplement IDE No. G900050 with additional data obtained from 50 new patients pursuant to the expansion of the Phase III investigation.

December 10, 1992 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH providing an Annual Report on IDE No. G900050. Includes a report from Dr. Gholam A. Peyman detailing the results from 75 additional patients in the expanded Phase III study. Provides updated lists of the 20 investigational sites.

January 4, 1993 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH in response to a request from Dr. Karam Batra to confirm the substance of discussions on December 22 and 23 regarding the number of subjects that have participated in the clinical investigation conducted pursuant to IDE No. G900050 (380 study subjects as of 12/92).

March 15, 1993 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH providing an interim report on 120 additional subjects and proposing that the Phase III study be expanded to include an additional 400 subjects (for a total of 1000 subjects) and 5 additional investigational sites.

April 7, 1993 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, announcing approval of the expansion of the clinical investigation under IDE No. G900050 by 400 additional subjects and 5 new institutions. The investigation is limited to 25 institutions and 1000 total subjects.

August 6, 1993 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH to supplement IDE No. G900050 with (1) an updated investigator and site list, (2) clinical data on 600 patients treated through May, 1993, (3) notification of a change in the data-reporting provisions of the protocol, and (4) sterilization information.

September 30, 1993 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH to supplement IDE G900050 with (1) a current list of investigators, (2) an update of the clinical data, and (3) an update of sterilization information. Requests an expansion of the Phase III portion of the investigation to include an additional 500 subjects, for a total of 1500, and an additional ten investigational sites, for a total of 35.

October 28, 1993 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, announcing FDA's approval of the proposal in the September 30, 1993 submission to expand the Phase III study to 1500 subjects and 35 institutions.

July 6, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH providing (1) an update on the status of IDE No. G900050; (2) announcing the temporary suspension of further shipment of VITREON®; and (3) proposing to establish a procedure to permit the limited use of VITREON® by participating investigators when necessary to protect the visual health and well-being of the subject in an emergency.

July 29, 1994 - Letter from Carol L. Patterson (Patterson Consulting Group, Vitrophage Consultant) to CDRH, reporting deviation from the investigational plan for emergency use (Cases 001 and 002).

August 3, 1994 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, requesting that FDA be notified of each "emergency use" of VITREON®.

August 25, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 003).

September 2, 1994 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Ms. Carol Patterson, Vitrophage Consultant, listing concerns and deficiencies involving the July 29, 1994 IDE supplement, which provided a statement of current indications for "emergency use" and two emergency use reports.

September 2, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH (1) responding to ODE's letter dated August 3, 1994; (2) providing an accounting of investigational devices shipped under IDE No. G9000050; and (3) proposing a limited clinical protocol (#VIT-NRGT/TR-101) to formalize the use of VITREON® under the "protocol deviation" conditions.

September 8, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 004 and 005).

September 14, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 006).

September 20, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 007-011).

September 22, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 012).

September 29, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 013-014).

September 30, 1994 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, concurring with the proposal to submit protocol #VIT-NRGT/TR-101 for review, and providing suggestions concerning study design and accountability.

October 4, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 006B).

October 6, 1994 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, responding to the September 8, 1994 report of deviations from the IDE plan, cases #004 and #005, and recommending measures to resolve the problem of investigator abuse of the emergency use of VITREON®.

October 14, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 015-018).

October 17, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 019).

October 19, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 020).

October 24, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH providing an IDE progress report, which notes that enrollment under the original protocol is complete and that Vitrophage currently is reanalyzing and reorganizing the data in a manner that will make it more useful to an assessment of efficacy and safety.

November 15, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 021).

November 23, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 022).

November 30, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 023 and 024).

December 2, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 025).

December 2, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH responding to issues addressed in ODE letters dated September 2, September 30, and October 6, 1994 and revised proposing a protocol for investigation #VIT-NRGT/TR-101.

December 6, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 026-028).

December 14, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 029).

December 15, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 030 and 031).

December 29, 1994 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, announcing additional deficiencies in the proposed protocol for investigation #VIT-NRGT/TR-101.

January 12, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 032).

January 19, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH responding to DOD's deficiency letter dated December 29, 1994 concerning proposed protocol #VIT-NRGT/TR-101. Submission includes revised protocol with changes that involve contraindications, post-operative monitoring and data collection, the list of study sites and investigators, a comparison to results of a silicone oil study, post-operative tamponades, data analysis issues, and miscellaneous other issues.

January 23, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 033).

February 8, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 034).

February 10, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 035).

February 13, 1995 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, approving the protocol submitted on January 19, 1995 (limited to 25 institutions and 75 subjects).

March 3, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case 034B).

March 15, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 036-039).

May 23, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 030B, 040-042).

June 5, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 043, 044).

June 14, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH reporting a deviation from the investigational plan that occurred at one site. Investigators at the site failed to remove VITREON® from seventeen patients, as the protocol required, no later than three to four weeks following the surgery.

July 14, 1995 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, responding to Mark A. Sievers' letter dated June 14, 1995, and requesting additional information regarding a deviation from the investigational plan that occurred at one investigational site.

August 23, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Cases 045, 046, 047).

August 29, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, responding to DOD's letter dated July 14, 1995, and providing requested information regarding a deviation from the investigational plan that occurred at one investigational site.

September 19, 1995 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, reporting that FDA reviewed the August 23, 1995 report of deviations from the IDE protocol and expressing concern that the medical monitoring of the emergency use protocol is deficient. Requests additional information regarding cases #045 and 046.

October 11, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting Notification of Withdrawal of IRB Approval.

November 2, 1995 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, requesting information concerning a protocol deviation that occurred at one of the investigational sites.

November 8, 1995 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH responding to DOD's September 19, 1995 letter concerning protocol deviations #045 and #046 and reviewing the procedure previously implemented for the medical review of deviation cases to verify compliance with protocol restrictions.

November 20, 1995 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, requesting a copy of the compliance procedure implemented for the medical review of deviation cases to verify compliance with protocol restrictions.

December 27, 1995 - Letter from Mark A. Sievers, Keller and Heckman to CDRH, responding to DOD's November 20, 1995 letter, and providing a copy of the compliance procedure implemented for the medical review of deviation cases to verify compliance with protocol restrictions.

January 4, 1996 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH, reporting deviation from the investigational plan for emergency use (Case #048).

May 9, 1996 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH (1) providing notification of termination of patient enrollment under Protocol #VIT-NRGT/TR-101; (2) requesting an extension of time to submit the next IDE progress report to allow the combination of the Final Report and the remaining subject follow-up data; and (3) responding to the ODE letter of November 2, 1995, by providing information on plans for following up on a protocol deviation that occurred at one of the investigational sites.

May 31, 1996 - Letter from Nancy C. Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman (1) acknowledging the termination of Protocol #VIT-NRGT/TR-101; (2) approving the request for an extension of time to submit the next IDE progress report to allow the combination of the Final Report with the remaining subject follow-up data; and (3) requesting specific follow-up data to be included.

July 2, 1997 - Letter from Mark A. Sievers, Keller and Heckman, to CDRH providing the Final Report concerning the clinical investigation conducted under IDE No. G900050, including a response to the request contained in DOD's May 31, 1996 letter requesting additional information.

July 29, 1997 - Letter from A. Ralph Rosenthal, Director, DOD, to Mark A. Sievers, Keller and Heckman, acknowledging completion of the Primary Clinical Study and termination of the investigation under Protocol #VIT-NRGT/TR-101. "FDA now considers this IDE application closed."

This chronology summarizes on written communications between the applicant and FDA during the regulatory review period. We note that, throughout this period, numerous telephone conferences were also held between the applicant and FDA regarding the status of the investigation being conducted under IDE No. G900050.

Chronology of Major Communications Between Applicant and FDA from December 6, 1991 to October 14, 1997

Re: PMA No. P910068

December 6, 1991 - Letter from Mark A. Sievers, Keller and Heckman, to Document Mail Center, Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), submitting an original Application for Premarket Approval (PMA) for VITREON®.

December 7, 1991 - Letter from Director, CDRH Premarket Approval Staff, to Mark A. Sievers, Keller and Heckman, assigning PMA Number P910068 to the December 6, 1991 PMA submission.

December 19, 1991 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 1), to PMA Document Mail Center providing a list of contacts and addresses for the (1) PMA applicant/distributor; (2) contract manufacturer; and (3) contract sterilizer, and correcting errors in data tables submitted with original PMA.

March 31, 1992 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 2), to PMA Document Mail Center providing report by Dr. Gholam A. Peyman updating clinical data on 50 additional patients in expanded Phase III clinical trial and providing copies of additional publications.

April 8, 1992 - Letter from Philip J. Phillips, Director, Program Operations Staff, Office of Device Evaluation (DOE), to Dr. Gholam A. Peyman, requesting additional manufacturing information.

October 7, 1992 - Letter from Mark A. Sievers, Keller and Heckman, to PMA Document Mail Center requesting an extension of time to respond to the request for additional manufacturing information set out in Philip J. Phillips' letter of April 8, 1992.

November 19, 1992 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 3), to PMA Document Mail Center providing (1) notification of change in name of PMA Sponsor; (2) a new manufacturing section (letter dated October 13, 1992 from Vitrophage's contract manufacturer, Air Products and Chemicals, Inc., containing information in response to Deficiency List in letter dated April 8, 1992 from Philip J. Phillips to Dr. Gholam A. Peyman); (3) an interim expanded Phase III report on clinical data from 75 additional patients; and (4) additional references.

March 15, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 4), to PMA Document Mail Center providing (1) Interim Report from Dr. Gholam A. Peyman on 120 additional subjects included in the expanded Phase III study; and (2) additional references.

March 19, 1993 - Letter from Philip J. Phillips, ODE, to Mark A. Sievers, Keller and Heckman, identifying deficiencies in the PMA manufacturing section and requesting additional information.

April 2, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 5), to PMA Document Mail Center providing (1) a Master Table of Contents covering all submissions in PMA No. P910068 as of April 2, 1993; (2) reprints of all data tables submitted thus far to PMA file (Tables I-XX) with separate table of contents; and (3) new tables providing statistical analysis of data on 500 patients from Phase I, II and III through February, 1993.

April 12, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 6), to PMA Document Mail Center providing a revised and expanded statistical report which supercedes and replaces the "Statistical Report" accompanying PMA Amendment No. 5 (dated April 2, 1993).

April 29, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 7), to PMA Document Mail Center providing additional information on the surgical procedure used in conjunction with VITREON® (as explained in a letter dated April 26, 1993 from Dr. Gholam A. Peyman).

June 7, 1993 - Letter from Philip J. Phillips, ODE, to Mark A. Sievers, Keller and Heckman, (1) announcing that CDRH determined that PMA No. 910068 "is sufficiently complete to permit a substantiative review and is, therefore, suitable for filing. The filing date is December 6, 1991, which is the date of CDRH receipt of the original PMA"; and (2) requesting five (5) copies of the full PMA file with the pages consecutively numbered.

June 22, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 8), to PMA Document Mail Center providing five (5) copies of the full PMA file, consecutively numbered, in response to the deficiency cited in letter dated June 7, 1993 from Philip J. Phillips to Mark A. Sievers.

June 25, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 9), to PMA Document Mail Center providing (1) an update of the results of the clinical investigation of the device; and (2) further information pertaining to the clinical use of the device and statistical analyses of the clinical data.

July 1, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 10), to PMA Document Mail Center providing a summary of a telephone conference with ODE officials concerning the need for additional information in the PMA file.

July 23, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 11), to PMA Document Mail Center providing (1) Device Master File (MAF) Authorization Letter from contract manufacturer; (2) addendum to the Statistical Analysis - Life Table Analysis; and (3) three extra copies of the current PMA File.

August 20, 1993 - Letter from Mark A. Sievers, Keller and Heckman, to Debra Y. Lewis, Branch Chief, Diagnostic and Surgical Devices Branch, Division of Ophthalmic Devices (DOD), ODE, requesting a meeting to discuss issues relating to the review of PMA No. P910068.

October 15, 1993 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 12), to PMA Document Mail Center providing additional manufacturing information in response to Philip J. Phillips' letter dated March 19, 1993.

December 7, 1993 - Facsimile from Patricia Fox, DOD-ODE, to Mark A. Sievers, Keller and Heckman, requesting additional manufacturing information on the production of VITREON®.

January 6, 1994 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 13), to PMA Document Mail Center providing (1) responses to the December 7, 1993 facsimile from Patricia Fox, DOD-ODE; (2) updated summary and statistical analysis of the results on first 700 patients in clinical study of VITREON®; (3) a response to a request for additional statistical information; (4) a separate volume from Dr. Emma Knight, DOD-ODE, consolidating the non-clinical safety information on perfluoroperhydrophenanthrene (PFPHP) (VITREON®); and (5) one computer disk with updated Statistical Analysis.

March 30, 1994 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 14), to PMA Document Mail Center providing information regarding the addition of a co-applicant for the PMA submission.

April 5, 1994 - Letter from Mark A. Sievers, Keller and Heckman, to Patricia Fox, DOD-ODE, providing information to be used in conjunction with the May, 1994 meeting of FDA's Ophthalmic Devices Panel.

April 15, 1994 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 15), to PMA Document Mail Center providing clarification of PMA Amendment No. 14 concerning the addition of a co-applicant for PMA No. P910068.

April 20, 1994 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 16), to PMA Document Mail Center providing information concerning a change in indications for use of VITREON®.

June 15, 1994 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 16 - inadvertently misnumbered - should be 17), to PMA Document Mail Center providing further clarification of PMA Amendment Nos. 14 and 15 concerning the addition of a co-applicant to PMA No. P910068.

July 29, 1994 - Letter from Dr. Susan Alpert, Acting Director, ODE, to Mark A. Sievers, Keller and Heckman, outlining deficiencies in the manufacturing and clinical information provided in PMA No. P910068 and requesting additional data.

January 12, 1995 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 18), to PMA Document Mail Center requesting an extension of time to file response to clinical deficiencies identified in FDA's letter dated July 29, 1994 letter.

January 24, 1995 - Letter from Nancy Brogdon, Interim Director, DOD, to Mark A. Sievers, Keller and Heckman, granting an extension of 90 days to respond to ODE's July 29, 1994 letter.

January 25, 1995 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 19), to PMA Document Mail Center providing (1) additional manufacturing, stability, and clinical information (in partial response to ODE's July 29, 1994 letter); and (2) a separate volume Toxicological Report of Non-Clinical Testing of VITREON® (separate volume).

March 14, 1995 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 20), to PMA Document Mail Center providing (in partial response to ODE's July 29, 1994 letter) (1) a process validation protocol; and (2) a stability protocol for VITREON®.

May 9, 1995 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 21), to PMA Document Mail Center providing a revised Clinical Data Report (Part I -- Cohort Group) (in partial response to ODE's July 29, 1994 letter).

May 25, 1995 - Letter from Kathy Lundsten, Program Operations Staff, ODE, to Mark A. Sievers, Keller and Heckman, requesting additional information concerning the process validation protocol submitted with PMA Amendment No. 20 (March 14, 1995).

May 26, 1995 -	Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 22), to PMA Document Mail Center providing (1) question-by-question responses to July 29, 1994 ODE deficiency letter (including references); and (2) a revised Clinical Data Report (Part II -- Non-Cohort Group).
July 11, 1995 -	Facsimile from Patricia Fox, DOD-ODE, to Mark A. Sievers, Keller and Heckman, providing a list of chemistry, microbiology, and toxicology deficiencies in PMA No. 910068 (5 pages of questions).
August 18, 1995 -	Facsimile from ODE-DOD reviewer providing a list of additional clinical deficiencies in PMA No. 910068.
August 29, 1995 -	(Submitted August 30) - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 23), to PMA Document Mail Center providing responses to the list of clinical deficiencies in ODE-DOD's facsimile dated August 18, 1995.
September 1, 1995 -	Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 24), to PMA Document Mail Center providing revised draft VITREON® Product Labels and Package Insert.
September 22, 1995 -	Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 25), to PMA Document Mail Center providing clinical additional information on subjects who were not included in the Clinical Reports provided in Amendment Nos. 21 and 22 (May 9, 1995 and May 26, 1995, respectively).
September 25, 1995 -	Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 26), to PMA Document Mail Center providing responses to list of chemistry, microbiology, and toxicology deficiencies in ODE-DOD's facsimile dated July 11, 1995.
September 25, 1995 -	Letter from Mark A. Sievers, Keller and Heckman, to PMA Document Mail Center, providing information to be used in conjunction with the October, 1995 meeting of FDA's Ophthalmic Devices Panel.

November 14, 1995 - Letter from Dr. Susan Alpert, Director, ODE, to Mark A. Sievers, Keller and Heckman, concluding that PMA No. 910068 is "approvable" and requesting the submission of additional information concerning chemistry, microbiology, toxicology, and product specifications.

May 9, 1996 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 27), to PMA Document Mail Center requesting an extension of time to file responses to ODE's deficiency letter dated November 14, 1995.

June 19, 1996 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 28), to PMA Document Mail Center providing a response to the chemistry, microbiology, toxicology, and product specification issues in ODE's November 14, 1995 deficiency letter.

July 29, 1996 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 29), to PMA Document Mail Center providing an attachment omitted inadvertently from revised Appendix N of PMA Amendment No. 28 (dated June 19, 1996).

August 21, 1996 - Letter from Kathy Lundsten, ODE, to Mark A. Sievers, Keller and Heckman, requesting additional information concerning the process validation protocol presented in PMA Amendment No. 28 (dated June 19, 1996).

November 15, 1996 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 30), to PMA Document Mail Center providing (1) a procedure for cytotoxicity testing of raw material; (2) response to August 21, 1996 Deficiency Letter from the Office of Compliance concerning the process validation protocol; (3) responses to other questions raised by ODE in telephone conferences on October 31, 1996 and November 7, 1996; and (4) additional manufacturing information for 3 batches of raw material proposed for manufacture into VITREON® (separate volume).

January 23, 1997 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 31), to PMA Document Mail Center providing (1) additional manufacturing information for 3 batches of raw material proposed for manufacture into VITREON®, and (2) responses to other questions raised by ODE in a telephone conference on January 16, 1997.

June 11, 1997 - Letter from Dr. Susan Alpert, ODE, to Mark A. Sievers, Keller and Heckman, indicating the PMA No. P910068 is "approvable" pending resolution of certain remaining issues.

July 11, 1997 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 32), to PMA Document Mail Center providing (1) response to June 11, 1997 Approvable Letter from ODE, including finished product testing results on first proposed commercial batch of VITREON®; and (2) responses to remaining miscellaneous ODE requests conveyed by telephone.

September 17, 1997 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 33), to PMA Document Mail Center providing (1) official submission of materials previously supplied to the ODE; (2) responses to additional miscellaneous ODE requests conveyed by telephone; and (3) change of official correspondent to Frederick A. Stearns (effective September 30, 1997).

September 25, 1997 - Letter from Mark A. Sievers, Keller and Heckman (PMA Amendment No. 34), to PMA Document Mail Center providing a revised VITREON® Package Insert, Vial Label, and Carton Label.

September 30, 1997 - Letter from Dr. Susan Alpert, Director, ODE, to Frederick A. Stearns, Keller and Heckman, announcing that PMA No. P910068 for VITREON® (perfluoroperhydrophenanthrene) Intraocular Fluid has been approved.

October 1, 1997 - Letter from Frederick A. Stearns, Keller and Heckman (PMA Amendment No. 35), to PMA Document Mail Center providing a revised VITREON® Package Insert (materials previously sent by facsimile to ODE reviewers on September 30, 1997).

October 14, 1997 - Letter from Frederick A. Stearns, Keller and Heckman (PMA Amendment No. 36), to PMA Document Mail Center providing final printed versions of the VITREON® Package Insert, Vial Label, and Carton Label (as required by ODE's September 30, 1997 approval letter).

October 14, 1997 - Letter from Deborah L. Falls, DOD-ODE, to Frederick A. Stearns, Keller and Heckman, acknowledging receipt of the PMA Amendment dated October 14, 1997.

This chronology summarizes only the major written communications between the applicant and FDA during the regulatory period. We note that, throughout this period, numerous telephone conferences were also held between the applicant and FDA regarding the status of FDA's review of PMA No. P910068.

12. In the opinion of the Applicant, U.S. Patent No. 4,490,351 is eligible for the length of extension sought, calculated in accordance with 37 C.F.R. §1.777 as described below. The date of submission of the IDE was October 11, 1989. Premarket approval (PMA) (for the approved device) was approved by the FDA Office of Device Evaluation on September 30, 1997.

CALCULATION OF PATENT TERM
EXTENSION FOR U.S. PATENT NO. 4,490,351
UNDER 37 C.F.R. §1.777

§1.777(c)	Determine length of regulatory review period as sum of:	
(c)(1)	Date that clinical investigation on humans was begun:	November 10, 1989
	Date application initially submitted with respect to device under §515:	December 6, 1991
	Total days of above period:	755 days
(c)(2)	Date application initially submitted with respect to device under §515(f)(5):	December 6, 1991
	Date application approved under §515(f)(6):	September 30, 1997
	Total days of above period:	2125 days
Length of regulatory review period as sum of §1.777(c)(1) and (c)(2):		2880 days

§1.777(d)	Determine term of patent as extended by:	
(d)(1)	Subtracting from the Regulatory Review Period	2880 days
(d)(1)(i)	Number of days in periods of (c)(1) and (c)(2) that were on and before the date the patent issued (i.e., on and before December 25, 1984):	0 days
(d)(1)(ii)	Number of days in periods of (c)(1) and (c)(2) during which it is determined under 35 U.S.C. 156(d)(2)(B) that Applicant did not act with due diligence:	0 days
(d)(1)(iii)	One half the number of days remaining in the period under (c)(1) after that period is reduced in accord with (d)(1)(i) and (ii):	
	(c) (1)	755 days
	minus (d)(1)(i)	0 days
	minus (d)(1)(ii)	0 days
	one-half of (c)(1)	376 days
Total (d)(1) extension		2504 days
§1.777(d)(2)	Adding the number of days determined in (d)(1) to the original term of the patent shortened by any terminal disclaimer:	
	Original expiration date:	March 15, 2002
	plus total (d)(1) days:	2504 days

Calculated (d)(2) expiration date:		January 21, 2009
§1.777(d)(3)	Adding 14 years to date of approval under §515	
	Date of approval plus 14 years	September 30, 2011
§1.777(d)(4)	Select earlier date of (d)(2) and (d)(3)	
	Selected earlier date:	January 21, 2009
§1.777(d)(5)(i)	Since original patent issued after September 24, 1984, add 5 years to original expiration date:	
	Original expiration date:	March 15, 2002
	plus 5 years:	March 15, 2007
(d)(5)(ii)	Select earlier date of (d)(4) and (d)(5)(i)	
	Selected earlier date	March 15, 2007
Date of extended expiration:		March 15, 2007

13. Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. Enclosed is a check made out to the Commissioner of Patents and Trademarks in the amount of $1,120 for payment of the fee for receiving and acting upon the application for extension.

15. Please direct all questions and correspondence to the undersigned attorney at the address noted below.

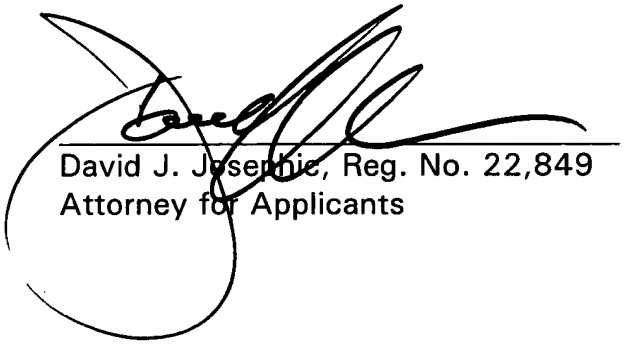
16. A duplicate copy of this Application for Patent Term Extension certified as such by the undersigned is enclosed.

17. A declaration of Applicant's patent attorney pursuant to 37 C.F.R. §1.740(b) is submitted herewith.

This Application for Extension of Patent Term is believed to comply with the requirements of 35 U.S.C. §156 and the applicable provisions of 37 C.F.R. Subpart F, §§1.740 et seq. Favorable action granting the extension sought herein is respectfully requested.

Respectfully submitted,

WOOD, HERRON & EVANS, L.L.P.



David J. Josephic, Reg. No. 22,849
Attorney for Applicants

2700 Carew Tower
Cincinnati, Ohio 45202-2917
Voice: (513) 241-2324
Fax: (513) 421-7269

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"Express mail" mailing label number EM032327137US

Date of Deposit November 25, 1997

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON DC 20231.

Cynthia J. Abaecherli
Name of Person Mailing Paper or Fee

Cynthia J. Abaecherli
Signature of Person Mailing Paper or Fee

Patent No: 4,490,351
Issued: December 25, 1984
Inventor: Leland C. Clark, Jr.
Title: METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS

Cincinnati OH 45202 November 25, 1997

BOX ASSIGNMENTS
Commissioner of Patents and Trademarks
Washington DC 20231

Sir:

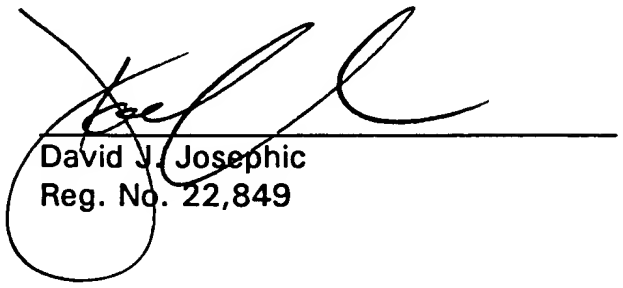
Enclosed for recordation in connection with the above identified patent are two assignment documents, together with recordation form cover sheets therefor and two checks each in the amount of $40.00, to be recorded in the following order:

(1) Assignment from Children's Hospital Medical Center to Leland C. Clark, Jr.

(2) Assignment from Leland C. Clark, Jr. to Vitrophage, Inc.

Respectfully submitted,

WOOD, HERRON & EVANS, L.L.P.



David J. Josephic
Reg. No. 22,849

2700 Carew Tower
Cincinnati OH 45202
(513)241-2324

EXPRESS MAIL NO. EM032327137US

OIPE JC10 NOV 25 1997 PATENT & TRADEMARK OFFICE

OIPE JC10 NOV 24 1997 PATENT & TRADEMARK OFFICE

FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Tab settings ⇨ ⇨ ⇨ ▼ ▼ ▼ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Children's Hospital Medical Center

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Leland C. Clark, Jr.

Internal Address: _____

Street Address: 218 Greendale Avenue

City: Cincinnati State: OH ZIP: 45220

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: April 14, 1992

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

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A. Patent Application No.(s)

B. Patent No.(s)

4,490,351

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Wood, Herron & Evans, L.L.P.

Internal Address: _____

Street Address: 2700 Carew Tower

441 Vine Street

City: Cincinnati State: OH ZIP: 45202

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number:

23-3000

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David J. Josephic
Name of Person Signing

Signature

11/25/97
Date

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments

INSTRUMENT OF CONFIRMATION OF ASSIGNMENT OF PATENT PROPERTY BETWEEN CHILDREN'S HOSPITAL MEDICAL CENTER AND LELAND C. CLARK, JR.

WHEREAS, CHILDREN'S HOSPITAL MEDICAL CENTER, an Ohio corporation, has heretofore on or about December 14, 1989, transferred and assigned to LELAND C. CLARK, JR., an individual residing at 218 Greendale Avenue, Cincinnati, Ohio 45220, the entire right, title and interest of all nature in, to and under U.S. Letters Patent No. 4,490,351, and the inventions secured thereby;

WHEREAS, it is desired by the parties hereto that said sale, transfer and assignment be confirmed by a separate instrument in writing;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that for good and valuable consideration the receipt and sufficiency of which is hereby acknowledged, said CHILDREN'S HOSPITAL MEDICAL CENTER does by these presents hereby declare and affirm that it by its then President William K. Schubert did heretofore on or about December 14, 1989, sell, transfer and assign unto said LELAND C. CLARK, JR., his legal representatives, successors and assigns, the entire right, title and interest in and to said Letters Patent, and in and to the subject matter disclosed therein, and any continuations, divisions, renewals, substitutes or reissues thereof, and in and to all Letters Patents Domestic and Foreign issued or to be obtained thereon, including all rights and interests with priority rights under the Paris Convention

for the Protection of Industrial Property, the International Patent Cooperative Union, European Patent Convention, Common Market Convention, or any other Convention or Union for each country of said Convention or Union, the same to be held and enjoyed by LELAND C. CLARK, JR., to the end of the term or terms for which said Letters Patents are or may be granted or reissued as fully and entirely as the same would have been held by said CHILDREN'S HOSPITAL MEDICAL CENTER had said sale, transfer and assignment not been made; together with all claims for damages by reason of past infringement of said Letters Patents, with a right to sue for, and collect the same for its own use and behoof, and for the use and behoof of its successors, assigns or other legal representatives; and said CHILDREN'S HOSPITAL MEDICAL CENTER does hereby ratify and confirm in all respects the aforesaid sale, transfer and assignment of said inventions, said applications for Letters Patents and said Letters Patents to LELAND C. CLARK, JR.

By _____
William K. Schubert, M.D.
President
CHILDREN'S HOSPITAL
MEDICAL CENTER

STATE OF OHIO)
) SS
COUNTY OF HAMILTON)

Sworn to and subscribed before me this 14th day of April, 1992.

(SEAL)

_____
Notary Public

DAVID J. JOSEPHIC, Attorney at Law
NOTARY PUBLIC - STATE OF OHIO
My Commission has no expiration
date. Section 147.03 O.R.C.

EXPRESS MAIL NO. EM032327137US

FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Leland C. Clark, Jr.

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Vitrophage, Inc.

Internal Address: _____

Street Address: 8643 W. Ogden Avenue

City: Lyons State: IL ZIP: 60534

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: July 19, 1993

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

B. Patent No.(s)

4,490,351

Additional numbers attached? ☐ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Wood, Herron & Evans, L.L.P.

Internal Address: _____

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441 Vine Street

City: Cincinnati State: OH ZIP: 45202

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number:

23-3000

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David J. Josephic — Name of Person Signing

Signature

11/25/97 — Date

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

INSTRUMENT OF CONFIRMATION OF ASSIGNMENT OF PATENT PROPERTY BETWEEN LELAND C. CLARK, JR. AND VITROPHAGE, INC.

WHEREAS, LELAND C. CLARK, JR., an individual residing at 218 Greendale Avenue, Cincinnati, OH 45220, has heretofore on or about March 16, 1993, sold, transferred and assigned to VITROPHAGE, INC., a corporation of the State of Illinois having a principal place of business at 8643 W. Ogden Avenue, Lyons, IL 60534, the entire right, title and interest of all nature in, to and under U.S. Letters Patent No. 4,490,351, and the inventions secured thereby;

WHEREAS, it is desired by the parties hereto that said sale, transfer and assignment be confirmed by a separate instrument in writing;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that for good and valuable consideration the receipt and sufficiency of which is hereby acknowledged, said LELAND C. CLARK, JR. does by these presents hereby declare and affirm that he did heretofore on or about March 16, 1993, sell, transfer and assign unto said VITROPHAGE, INC., its legal representatives, successors and assigns, the entire right, title and interest in and to said Letters Patent, and in and to the subject matter disclosed therein, and any continuations, divisions, renewals, substitutes or reissues thereof, and in and to all Letters Patents Domestic and Foreign issued or to be obtained thereon, including all rights and interests with priority rights under the Paris Convention

for the Protection of Industrial Property, the International Patent Cooperative Union, European Patent Convention, Common Market Convention, or any other Convention or Union for each country of said Convention or Union, the same to be held and enjoyed by VITROPHAGE, INC. to the end of the term or terms for which said Letters Patents are or may be granted or reissued as fully and entirely as the same would have been held by said LELAND C. CLARK, JR. had said sale, transfer and assignment not been made; together with all claims for damages by reason of past infringement of said Letters Patents, with a right to sue for, and collect the same for its own use and behoof, and for the use and behoof of its successors, assigns or other legal representatives; and said LELAND C. CLARK, JR. does hereby ratify and confirm in all respects the aforesaid sale, transfer and assignment of said inventions, said applications for Letters Patents and said Letters Patents to VITROPHAGE, INC.

By Leland C. Clark, Jr.
Leland C. Clark, Jr.

STATE OF OHIO)
) SS
COUNTY OF HAMILTON)

Sworn to and subscribed before me this 19th day of July, 1993.

(SEAL)

Notary Public

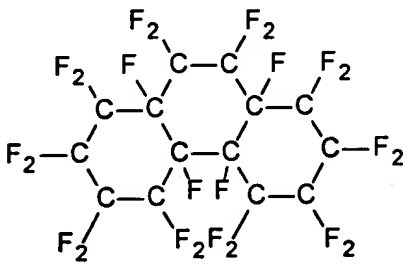
DAVID J. JOSEPHIC, Attorney at Law
NOTARY PUBLIC - STATE OF OHIO
My Commission has no expiration
date. Section 147.03 O.R.C.

Ex. B

VITREON® **℞**
(perfluoroperhydrophenanthrene)

DESCRIPTION

VITREON® sterile intraocular fluid is a purified perfluorocarbon liquid comprised of perfluoroperhydrophenanthrene (PFPHP) ($C_{14}F_{24}$), with perfluoro-n-butyldecalin and related perfluorinated isomers. PFPHP has the following chemical structure:



VITREON has the following chemical and physical properties:

- Optically clear	
- Immiscible with water	
- Easily injectable	
- Molecular Weight	624.12
- Specific Gravity	2.03
- Surface Tension (dynes/cm, 25°C)	23.9
- Refractive Index	1.3340
- Vapor Pressure (torr @ 37°C)	0.35
- Viscosity (centistoke @ 25°C)	7.80
- Boiling Point (°C)	215

VITREON contains no preservatives.

VITREON is supplied in 6-ml single-dose glass vials capped with a rubber stopper. Each single-dose vial is packaged in an individual carton.

The finished product testing for each batch of VITREON includes tests and specifications to limit potential impurities. Each batch of VITREON is also tested for particulate matter and bacterial endotoxins with strict limits appropriate for injectable ophthalmic products.

INDICATIONS FOR USE

VITREON is indicated for use as an intraoperative surgical aid during vitreoretinal surgery in patients with primary and recurrent complicated retinal detachments. Complicated cases include giant retinal tear or retinal dialysis, proliferative vitreoretinopathy, proliferative diabetic retinopathy, tractional retinal detachments, and blunt or penetrating ocular trauma.

CONTRAINDICATIONS

- VITREON is contraindicated as a vitreous replacement.

WARNINGS

- VITREON should not be injected directly into the anterior chamber, or be removed from the vitreous cavity through the anterior chamber, as corneal endothelial cell damage may occur. VITREON cannot be removed completely via the anterior chamber.

- At the conclusion of the surgical procedure, VITREON must be removed completely from the vitreous chamber, via the pars plana, and replaced with an appropriate vitreous substitute.

PRECAUTIONS

- Directions for Use of VITREON should be followed closely.

- Animal tests indicate that VITREON may be physically irritating to the cornea when there is direct contact. Corneal endothelial cell damage can occur in as few as three days after direct contact. Any VITREON in the anterior chamber must be removed. A conscientious effort should be made to remove all VITREON at the conclusion of surgery in accordance with the Directions for Use. If a small amount (0.5 DD area) of VITREON remains in the vitreous chamber at the conclusion of surgery, the patient must be carefully monitored until any residual VITREON has completely dissipated to prevent entry into the anterior chamber in aphakic eyes.

- Posterior retinal slippage occurred in 7.7% of patients with giant retinal tears in the cohort group (See Directions for Use). To help prevent slippage, gradually remove the VITREON under air-VITREON exchange or silicone-VITREON exchange.

- The use of VITREON intraoperatively in patients with complicated retinal detachments in conjunction with large posterior breaks associated with residual traction may allow migration of VITREON into the subretinal space. While such migration occurred infrequently in the clinical studies, VITREON should be removed via these retinal breaks if it enters the subretinal space. (See Directions for Use)

- As with any invasive procedure, there is the possibility of infection. Aseptic techniques must be strictly adhered to.

- VITREON is supplied in a sterile vial intended for single use only for a single patient.

- VITREON should not be re-sterilized and unused portions should be discarded.

- Do not mix VITREON with any other substances prior to injection.

- VITREON should be discarded following the expiration date.

- The safety and effectiveness of long-term use of VITREON post-operatively have not been established.

ADVERSE REACTIONS AND COMPLICATIONS

The data supporting the rates of occurrence of complications were derived from a U.S.-based multicenter clinical trial. Data were divided into two segments and were analyzed separately. The "cohort" group consisted of 343 patients evaluated for safety and effectiveness parameters. The "non-cohort" group included data on 1241 additional patients evaluated for safety parameters only. In the following discussion, occurrence rates are reported by the specific group in which the complication occurred.

- Rate of retinal redetachment:
  Overall, 40.3% of the cohort subjects had a redetachment during the postoperative period. The rate of retinal redetachment in the non-cohort group was 34.4%. Although more of the subjects were followed for a greater length of time in the cohort group, the majority of redetachments observed occurred prior to four months postoperatively in both groups.

- Proliferative Vitreoretinopathy (PVR):
  PVR was present preoperatively in 41.6% of the cohort group and 50.1% of the non-cohort.
  PVR occurred in 20.3% of the cohort (11.9% of the non-cohort) subjects from whom VITREON was removed.

The following adverse reactions related to the use of VITREON were observed:

COHORT GROUP

- Intraoperative subretinal VITREON migration (preoperative diagnosis of retinal detachment) 0.9%

- Postoperative residual VITREON 9.0%

OVERALL GROUP

- Postoperative residual VITREON 6.5%

The following complications reported by the investigators are general complications that are observed in complex vitreoretinal surgery, and were not associated specifically with the use of VITREON:

COHORT GROUP

- Corneal disorders (including bands and keratopathy) 17.9%
- Corneal edema 12.4%
- Anterior chamber abnormalities (fibrin in AC, hyphema) 18.2%
- Elevated IOP (181-360 days follow up) 0.7%
- Elevated IOP > 25 mmHg was observed in 19.9% of subjects in the first month, decreasing to 1.9% in the 4 to 6 month follow up.
- Hypotony (181-360 days follow up) 25.9%
- Iris abnormalities 8.5%
- Cataract formation in phakic eyes 3.0%
- Intraoperative retinal slippage 7.7%
- Progression to "no light perception" (NLP) (181 - 360 days follow up) 6.1%

OVERALL GROUP

- Corneal disorders (including bands and keratopathy) 13.7%
- Corneal edema 7.5%
- Anterior chamber abnormalities (fibrin in AC, hyphema) 8.3%
- Elevated IOP (181 - 360 days follow up) 2.2%
- Hypotony (181-360 days follow up) 17.5%
- Iris abnormalities 5.0%
- Progression to "no light perception" (NLP) (181 - 360 days follow up) 4.9%
- Other:
  In addition to the complications

above, other less commonly occurring reactions reported in the combined cohort and non-cohort groups (1630 subjects), in more than 2% of patients and ranked by frequency of occurrence, included: hyphema; various membrane related conditions (pucker, epiretinal membrane, retinal fibrosis, gliosis, fibrosis, subretinal fibrosis, epimacular membrane, maculopathy) subretinal fluid or blood; corneal epithelial defects; vitreous hemorrhage; lens-related problems; choroidal detachment; retinal folds. The following complications occurred at rates of less than 2% in the patients in the combined cohort and non-cohort groups: retinal hemorrhage; macular/retinal edema; macular folds; choroidal folds; choroidal hemorrhage; giant tear; retinal striae/ macular striae; age-related macular degeneration (AMD); pupil disorders; extra-ocular problems.

DIRECTIONS FOR USE

Caution: The outer surfaces of the container are not sterile. Carefully follow directions below for loading VITREON. Remove the VITREON vial from the carton, flip off cap to remove top of crimp seal and expose target surface of the stopper, disinfect exposed stopper surface, and load the VITREON into a Luer-Lok screw syringe. Avoid introduction of air bubbles into the VITREON by careful withdrawal or decanting of the fluid into the syringe. Place the syringe on a sterile tray.

The surgical procedure consists of a standard 20-gauge three-port pars plana vitrectomy. Once partial or total vitrectomy is completed, inject 0.5-4 ml VITREON through a blunt 20- to 27-gauge needle over the optic disc. In the case of a giant tear, injection must be over the retina, or under the retinal flap if it is in a folded position. A partial air-fluid exchange may be necessary during the injection process in order to tamponade the peripheral retina.

Upon completion of VITREON injection, additional procedures such as endolaser photocoagulation, internal or external cryopexy, and membranectomy may be performed.

Do Not Resterilize VITREON

Post-Procedure

VITREON must be removed at the conclusion of the operative procedure.

VITREON can be removed by "passive" flow through a flute needle or active suction while the vitreous cavity is filled with air or infusion fluid. The surface of VITREON is easiest to see

during air-VITREON replacement which ensures a more complete removal of VITREON. Remove VITREON only through the pars plana. Do not remove through anterior chamber. Upon removal, multiple fluid washings must be performed to maximize complete evacuation. It may then be replaced by an approved vitreous substitute. Any VITREON in the anterior chamber must be removed immediately using standard techniques. (See Precautions)

The patient should be monitored closely by the physician for the development of routine postoperative complications and be scheduled for follow up at regular intervals.

The Use of VITREON

Properties

VITREON contains inherent physical properties necessary for a desirable denser-than-water temporary vitreous substitute. It is immiscible with water, optically clear, radiopaque, easily injected and removed through a small-bore (20- to 25-gauge) needle. Its low vapor pressure permits air travel without the danger of gas formation in case a small amount of residual VITREON remains in the eye. VITREON has a high surface tension (23.9 dynes/cm @ 25°C) and a high viscosity (7.80 cs), two important characteristics to reduce bubble formation and migration through small retinal holes. Intraoperative subretinal migration has been seen in only 0.9% of retinal detachment cases in the cohort group.

Toxicity and Metabolism

VITREON is a biologically inert substance. There are no known biological enzymes which metabolize the carbon-fluoride bonds in perfluorocarbons.

VITREON is non-pyrogenic, non-mutagenic and non-irritating in the posterior chamber.

Experimental studies demonstrated that VITREON has no toxic effect on tissue culture-grown cells. *In vivo* studies in rabbits have shown no acute toxic or inflammatory reactions for up to 6 weeks. *In vivo* studies in primates have shown that VITREON has no toxic effects up to 162 days, although emulsification started at approximately 72 days.

Animal tests indicate that VITREON may be physically irritating to the cornea when there is direct contact. Corneal damage can occur in as few as three days after direct contact. Any VITREON in the anterior chamber must be removed. A conscientious effort should be made to remove all VITREON at the conclusion of surgery in accordance with the Directions for Use. Small amounts of residual

VITREON (0.5 DD) in the vitreous cavity were observed in the clinical studies but were not associated with any complications or adverse reaction. (See Precautions)

General Use

VITREON should be injected through a 20-gauge needle over the optic disc, forcing the subretinal fluid anteriorly, where it escapes through an anteriorly located retinal hole.

VITREON is then removed using a flute needle or active aspiration through a 20-gauge blunt cannula. The tip of the cannula is brought over the surface of the retina. Intermittent air and fluid exchanges are performed to maximize removal of all the VITREON.

Removal of VITREON from the subretinal space can be done through existing retinal breaks or a posterior retinotomy. Infusion of irrigating solution through the infusion cannula is performed simultaneously with removal of the VITREON through an extrusion needle inserted through the break or retinotomy, until complete removal of the VITREON is achieved. After removal, the break or retinotomy is coagulated with endolaser. The retina can then be tamponaded with appropriate vitreous substitutes.[1]

Intermittent air and fluid exchanges are performed to remove all VITREON. If small amounts (< 0.5 DD) of residual VITREON are left in the vitreous cavity they should be monitored and their time of complete dissipation noted. Larger amounts should be removed. In aphakic eyes in which there is no barrier (capsule) to the anterior chamber, any residual VITREON must be removed to protect against migration to the anterior chamber.[1]

In GIANT RETINAL TEARS[2]

VITREON facilitates repair of a giant tear (to hydrokinetically manipulate the retina back into position) with the patient in a supine position.

After vitrectomy and adequate removal of retinal traction, VITREON is injected with a blunt 20-gauge to 27-gauge needle over the optic disc. The subretinal fluid is pushed in a posterior-to-anterior direction and out to the edge of the giant retinal tear.

The clinical studies have shown that retinal slippage occurred in 7.7% of patients (cohort group) with giant retinal tears. When slippage of the retina occurs, the mechanical action of the reinjected VITREON elevates the retina into proper apposition with the retinal pigment epithelium (RPE) and unfolds the retinal flap of the giant tear.

When the retina is completely flat, endolaser photocoagulation, cryopexy, or a combination of these procedures is performed. At this point, a decision is made to replace the VITREON intraoperatively with either sulfur hexafluoride (SF_6) (15% to 20%), perfluoropropane (C_3F_8) (10% to 15%), or silicone oil for a longer tamponading effect.

To remove the VITREON from the eye, an air-VITREON exchange is followed by three or four partial fluid-VITREON exchanges to remove any residual VITREON. A silicone-air exchange is then performed, or the air-filled eyes are flushed with 25 cc 20% SF_6 or C_3F_8. An encircling scleral buckle can be placed.

In PROLIFERATIVE VITREORETINOPATHY (PVR)[3]

The use of VITREON permits initial membrane dissection and intraoperative retinal stabilization of posterior PVR.

A three-port pars plana technique is used. Using a pick, an attempt is made to create an edge in the membrane close to the optic nerve head. After initial dissection, a small amount of VITREON is injected over the optic nerve, which flattens the adjacent retina. The membrane dissection continues from the posterior to the anterior direction.

VITREON stabilizes the posterior retina by forcing subretinal fluid out of anteriorly located retinal breaks. It facilitates dissection of posterior PVR. Anterior PVR can then be dissected and removed subsequently while the posterior retina is attached and kept in place by the weight of the VITREON.[1, 3]

After reattachment of the retina, the VITREON can be exchanged either with gas or silicone oil to provide a longer term tamponading effect.[1, 3]

In OCULAR TRAUMA[4]

Traumatic eye injuries are often accompanied by vitreous hemorrhage and retinal detachment caused by peripheral tears. These injuries may include cases of giant retinal tears, large areas of missing retina and/or where there is the need to perform extensive retinotomy in the presence of extensive traction or retinal scarring. After the diagnosis is established by the use of ultrasound, the surgeon must decide when to intervene surgically.

As soon as the surgeon cuts the detached posterior hyaloid, the vitrectomy instrument is removed and a 20-gauge blunt needle connected to a syringe with 5 ml VITREON is inserted in the vitreous cavity. The tip of the needle is passed through the opening in the posterior hyaloid membrane in the

retrohyaloid space. VITREON is injected gradually into the space between the posterior hyaloid membrane and the detached retina. The height of the infusion bottle is lowered as the vitreous cavity gradually fills with VITREON. As the VITREON fills the posterior part of the vitreous cavity and flattens the posterior retina, the subretinal fluid is pressed out from the anteriorly located retinal hole or tears. During this procedure, the entire vitreous containing the hemorrhage is pushed forward toward the anterior part of the vitreous cavity. At this stage, the vitrectomy instrument is reinserted into the vitreous cavity and vitrectomy is performed until the majority of the vitreous opacities are removed.

Endolaser or cryotherapy is applied to the retinal hole. VITREON can be removed by air-VITREON or VITREON-silicone exchange. The operation concludes with further endolaser application to the peripheral retina, and suturing of an encircling band to the sclera to support the anterior retina.[1]

HOW SUPPLIED

VITREON is supplied in 6-ml single-dose vials capped with a rubber stopper. Each single-dose vial is packaged in an individual carton.

For intraocular use only.

STORAGE

The product should be stored at room temperature (20°C - 25°C).

REFERENCES

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4. Desai UR, Peyman GA, Harper CA III: Perfluorocarbon liquid in traumatic vitreous hemorrhage and retinal detachment. Ophthalmic Surg 24:537-541, 1993.

VITREON is a registered trademark of Vitrophage, Inc.

VITREON is manufactured for Vitrophage, Inc., 8643 W. Ogden Avenue, Lyons, IL 60534

Rev. 9/97

EX. C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Frederick A. Stearns
Counsel for Vitrophage, Inc.
c/o Keller and Heckman LLP
1001 G Street, N.W.
Suite 500 West
Washington, DC 20001

SEP 30 1997

Re: P910068
VITREON® (Perfluoroperhydrophenanthrene) Intraocular Fluid
Filed: December 6, 1991
Amended: December 19, 1991; March 31, October 7, November 23, 1992; April 2, 13, and 29, June 22 and 25, July 2 and 23, August 20, September 13, October 15, and November 1, 1993; January 7, March 30, April 15, 19 and 20, and June 15, 1994 January 12 and 25, March 14, May 9 and 26, August 30, September 1 and 25, 1995; January 29, March 20, May 9, June 19, July 30 and 31, and November 18, 1996; and January 23, July 14, and September 17 and 25, 1997

Dear Mr. Stearns:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of the premarket approval application (PMA) that you submitted on behalf of your client, Vitrophage, Inc. for VITREON® (Perfluorophenanthrene) Intraocular Fluid. This device is indicated for use as an intraoperative surgical aid during vitreoretinal surgery in patients with primary and recurrent complicated retinal detachments. Complicated cases include giant retinal tear or retinal dialysis, proliferative vitreoretinopathy, proliferative diabetic retinopathy, tractional retinal detachments, and blunt or penetrating ocular trauma. We are pleased to inform you that the PMA is approved for a single batch (Batch # 672-45-0001) of the finished product packaged in sterile 6 mL vials. This approval is subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

You have informed FDA in a meeting on February 6, 1996, that you will be changing the raw material supplier. Your approval is limited to batch # 672-45-0001, therefore, if you wish to market other batches using a new raw material supplier, you must submit and receive FDA approval for a PMA supplement which supports the change in the raw material supplier.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 2 years for the 6 ml vials. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Page 2 - Mr. Frederick A. Stearns

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Eleanor M. Pelton or James F. Saviola, O.D., at (301) 594-1744.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

EX. D

United States Patent [19]

Clark, Jr.

[11] **Patent Number: 4,490,351**

[45] **Date of Patent: Dec. 25, 1984**

[54] **METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS**

[75] Inventor: **Leland C. Clark, Jr.**, Cincinnati, Ohio

[73] Assignee: **Children's Hospital Medical Center**, Cincinnati, Ohio

[21] Appl. No.: **358,055**

[22] Filed: **Mar. 15, 1982**

[51] **Int. Cl.**[3] **A61K 49/04; A61K 31/025**

[52] **U.S. Cl.** **424/5**; 424/352

[58] **Field of Search** 424/5, 352

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Vygantas, Charles M., "Octafluorocyclobutane (C_4F_8) Gas as Vitreous Replacement", *Vitreous Surgery and Advances in Fundus Diagnosis and Treatment*, 1977, pp. 423–425.

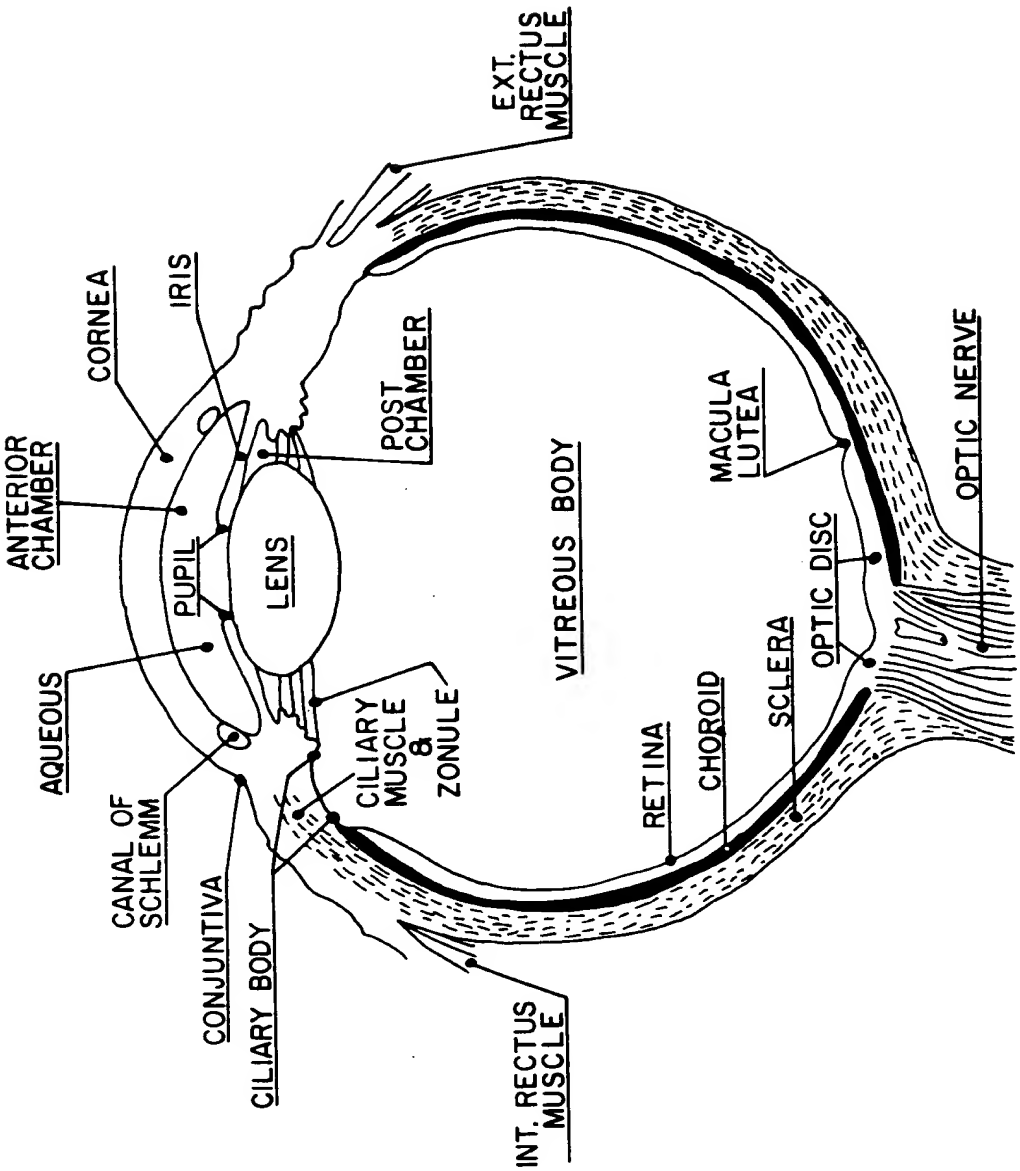
Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Wood, Herron & Evans

[57] **ABSTRACT**

Liquid perfluorocarbons and substituted derivatives thereof are used as fluid substitutes for the vitreous or the aqueous of the eye. These liquids are also used to transparentize the cornea or lens when either becomes opacifed due to degeneration or cataract formation. Methods involving the use of these liquids during retinal surgery or diagnostic procedures of the eye are also disclosed.

30 Claims, 1 Drawing Figure


EXT. RECTUS MUSCLE
CORNEA
IRIS
POST CHAMBER
ANTERIOR CHAMBER
PUPIL
LENS
VITREOUS BODY
MACULA LUTEA
OPTIC NERVE
OPTIC DISC
SCLERA
AQUEOUS
CILIARY MUSCLE & ZONULE
RETINA
CHOROID
CANAL OF SCHLEMM
CONJUNTIVA
CILIARY BODY
INT. RECTUS MUSCLE

METHODS OF TREATING DISORDERS OF AN EYE WITH LIQUID PERFLUOROCARBONS

BACKGROUND OF THE INVENTION

The eye, which is responsible for vision, is probably the most remarkable organ in animals. It is comprised of many complex components, for example, cornea, aqueous humor, lens, vitreous and retina, with each having its own highly specialized function contributing significantly to the overall visual experience. Unfortunately, each section of the eye is susceptible to well-known pathological disorders which can reduce the quality of vision and/or resulting in partial or total blindness. Such pathological processes comprise vitreous liquefaction and opacification, retinal detachment, glaucoma, and opacification of the lens and cornea.

The vitreous is a remotely oxygenated transparent mass that in most animals is physically a gel-like substance. It consists predominantly of water and fills the posterior chamber of the eye. The vitreous functions to give shape to the eye, transmit light, and form a semi-solid support for the retina against the choroid. When the vitreous is physically altered or becomes opaque, permanent blindness can develop. For example, should the vitreous partially liquify, as it often does with age, its supporting capability is diminished and retinal detachment may result. It is well appreciated that retinal detachment is the leading cause of blindness in the United States.

Furthermore, the vitreous may become opaque as a direct consequence of cellular infiltration or hemorrhage. Cellular infiltrations are common in a number of inflammatory processes of tissue surrounding the vitreous. As a result of inflammation, opacification degeneration of the vitreous may be seen. Vitreous hemorrhage is also very common, particularly in diabetics, and occurs when the retina ciliary body ruptures and hemorrhages into the vitreous developing large opaque areas. Unlike most other tissue, however, the vitreous is avascular and does not contain significant macrophages. Therefore, if foreign agents or blood penetrate into the vitreous, they may permanently remain in the vitreous thereby leading to partial or total vision impairment. In either disease process, liquefaction or opacification of the gel-like substance, vitreous replacement with a suitable substitute is required.

For several years, surgical removal and replacement of the vitreous with a less than optimal substitute has been known. Vitreous replacement has been accomplished by a variety of liquids including salt solutions, vitreous humor from animals, spinal fluids and other substances thought to have desirable properties. *Survey of Ophthalmology:* "A Review Of Substances And Techniques Of Vitreous Replacement" by G. H. Peyman, E. S. Ericson and D. R. 17:41-51, May, 1972. Silicone oils (dimethylsiloxanes of various viscosities) have been used for partial replacement of vitreous humor with success but have doubtful application because of pathological changes after long term replacement. *New England Journal of Medicine:* "Alloplasty In Surgery Of The Eye" by W. Stone, Jr., 258:486-490, 1958. There also have been reported results from the use of lyophilized vitreous, pure hyaluronic acid, or polygeline and the use of collagen is still in its experimental stage. Gloor, B.P.M.P.IN: Moses R. A. (Pd.) *alters physiology of the eye.* Clinical application. 7th Ed. St. Louis: C. V. Mosby Company, p. 270 (1971). *Biochimica et Biophysica Acta:* "Studies On Hyaluronic Acid". The Preparation And Properties Of Rooster Comb Hyaluronic Acid" by D. A. Swann, 156: 17-30 (1968) and U.S. Pat. No. 4,141,973, issued Feb. 27, 1979 to Balazs.

Out of the presently available vitreous replacements, salt solutions, silicone oils and hyaluronic acids are predominantly used even though they are less than optimal substitutes with each having its own major disadvantages. Salt solutions are not readily compatible with the retina or the optic nerve, yielding some disintegration of vision, changes at the end of the optic nerve and retinal unhealthiness. Silicone oils, in addition to their toxicities, also tend to emulsify and break-off into droplets, a process often called "fish-egging", thereby enhancing their turbidity. Finally, hyaluronic acid is very expensive, difficult to produce and has a fixed viscosity. Since hyaluronic acid is derived from rooster combs, its supply is limited.

Most knowledge of present vitreous replacement concerns the uses of gases such as air, nitrogen, and sulfurhexafluoride. The first fluorocarbon to be used as a gas in the vitreous was octafluorocyclobutane or perfluorocyclobutane. *Archives of Ophthamology:* "Octafluorocyclobutane And Other Gases For Vitreous Replacement" by C. M. Vygantas, G. A. Peyman, M. J. Daily and E. S. Ericson 90:235-236, 1973. Other perfluorocarbon gases more recently tested are perfluoromethane, perfluoroethane and perfluoropropane. *Archives of Ophthamology:* "Intravitreal Longevity Of Three Perfluorocarbon Gases" by H. Lincoff, J. Mardirossian, A. Lincoff, P. Ligett, T. Iwamoto and F. Jakobjec, p. 1610, 1980. Perfluoro-n-butane and perfluoroisobutane have also been studied. *Vitreous Surgery And Advances In Fundus Diagnosis And Treatment,* "Octafluorocyclobutane (C_4F_8) Gas As Vitreous Replacement" by C. M. Vygantas pp. 423-425, 1975. These gases are being used because they are biologically inert, insoluble in water and pass through membranes very slowly. They, therefore, equilibrate with blood gases (O_2, CO_2, N_2) in the vitreous and reach an equilibrium condition after hours or days. The equilibrium finally reached is a function of the partial pressure of the particular gas as well as the blood gases. However, since perfluorocarbon gases are compressible, they will remain in an equilibrium state only as long as the gas pressure is essentially unchanged. For example, the gases would increase in volume during an airplane flight while their volume would probably also change during anesthesia because most anesthetic gases rapidly diffuse through body tissues. Fluorinated anesthetics might represent particularly complicated gas-vapor level equilibrium. Because of these undesired properties, among others, perfluorocarbon gases are less than optimal as vitreous replacements. However, in spite of considerable work reported in connection with vitreous replacement, as set forth herein above, there is no ideal gelatinous substitute for the complex glycoprotein structure of the vitreous body. Known vitreous replacements are not completely satisfactory because they may cause post-operative complications resulting in total blindness. Vitreous substitutes, thus, have somewhat fallen into disrepute because basic researchers have had difficulty introducing a substitute that is clear, inert, well tolerated, and remains viscous long enough.

The retina comprises the innermost tunic of the eyeball containing the nervous elements for reception of visual stimulae. The phenomenon of detachment of the

retina consists of physical separation of the retina from its juxtaposition to the choroid. The most important factor contributing to retinal detachment is liquefaction and shrinkage of the vitreous, commonly known as vitreous retraction. In addition, vitreous retraction generated by vitreous shrinkage may produce retinal tear with or without retinal detachment. There are presently three methods of treatment for retinal tear with or without retinal detachment. The first consists of scleral buckling (forcing the anterior wall of the choroid against the posterior side of the retina) which utilizes an external encircling band in retinal tears and detachments. Also, removal of the entire vitreous gel from the vitreous cavity may be utilized in retinal detachment. However, this procedure is utilized only in extreme cases. The third method requires the patient to lie on his ventral surface while the physician introduces into the posterior chamber an air bubble (having a specific gravity less than vitreous fluid) in order to force the detached retina back against the choroid. Moreover, the patient must remain on his ventral surface during the early recovery stage, perhaps for many days. All three forms of treatment appear to be quite inconvenient to the patient as well as to the physician, and constitute somewhat extreme methods of treatment.

The aqueous humor is the fluid produced in the eye which fills the anterior chamber, located between the cornea and the lens. Because aqueous humor is being produced constantly, its rate of formation and exit from the eye is directly related to the steady straight level of intraocular pressure. In "glaucoma", elevated intraocular pressure is related to the eye's reduced capability to facilitate outflow of aqueous humor. Thus, the abnormally high pressure squeezes against the retina, occluding circulation in the choroid and retina, the optic disk becomes distorted and concave, and blindness results. The primary treatment for glaucoma presently is to medicate the eye with a drug that decreases the rate of aqueous humor formation. The present course of therapy is to suppress the rate at which aqueous humor is formed. But it appears possible to totally replace the aqueous humor in glaucoma. The problem with replacing aqueous humor, however, is to find a suitable substance. Heretofore, there have been no attempts to replace the aqueous humor with substitutes.

The cornea and lens are normally transparent to provide refracting surfaces for the optical system of the eye. Any change in the transparency of the cornea or the lens will seriously interfere with the clarity of the retinal image. Nevertheless, the cornea and lens are subject to loss of transparency and will develop opacity depending upon the disease process as to which each may be affected. Presently, the opaque areas in the cornea and lens are surgically removed. In addition, the lens is often totally removed, for example in cataract surgery. The undesirable complications that can develop from surgical treatment of opaque areas within the cornea and lens are well known. Moreover, if surgical removal of the opaque areas is successful, vision will probably remain impaired and even possibly incorrectable.

It is apparent from the above brief overview of various disorders of the eye and the current state of knowledge that there are critical needs which must be met, and problems to be solved, so that the precious phenomenon of eyesight may be either restored or preserved.

SUMMARY OF THE INVENTION

Liquid perfluorocarbons and substituted derivatives thereof have been found to be substitutes for the vitreous or aqueous. Also, such liquids can be forced into opaque areas within the cornea or lens and transparentize them so that vision may be restored. These liquids can be introduced into the vitreous to treat retinal tears (rips) or detachments. Other radiopaque liquids can be introduced into the eye for diagnostic purposes.

This invention is directed to the use of perfluorocarbon liquids and substituted derivatives thereof in ophthalmological disorders. Perfluorocarbons have been found to be advantageous substitutes for the liquids within the eye as well as transparentizing agents for the cornea and lens. These liquids have been introduced into eyes of experimental animals to function as vitreous and aqueous humor substitutes, and as transparentizing agents. They have been proven to be useful substitutes, and experimental animals treated with these liquids not only maintain normal vision, but can live normal lives after treatment. Furthermore, the perfluorocarbons surprisingly are retained indefinitely within the eye, particularly within the cornea and lens, as well as the posterior and anterior chambers. These and other remarkable discoveries will become further understood in the details which follow.

The perfluorocarbon liquids are preferably transparent or light transmissive, inert, remain viscous indefinitely, and can be chemically designed to have certain viscous and elastic properties. Moreover, neat fluorocarbon liquids generally dissolve at least 20 times as much oxygen and carbon dioxide as water, aqueous or vitreous, have zero oncotic pressure (like vitreous), are more dense than water, are immiscible with blood or water, and can be sterilized by autoclaving. Thus, these liquids are comprised of unusual chemical and physical properties endowing them with unique, unexpected and advantageous uses in ophthalmological disorders. Exemplary of suitable perfluorocarbon liquids and substituted derivatives are perfluorooctylbromide (PFOB), perfluoro 1-methyldecalin (PP9), and perfluoro 1, 3-dimethyladamantane and perfluorotrimethylbicyclo[3.3.1.]nonane mixtures (DAWN).

Thus, this invention is predicated in part upon the discovery that perfluorocarbon liquids are ideal as substitutes for the vitreous and aqueous humor. They are inert, transparent or light transmissive, and well tolerated. As such, they fulfill outstanding needs in eye disorders such as replacement of cloudy or opaque vitreous after hemorrhages and inflammatory processes. Another important discovery involved in this invention is that these liquid perfluorocarbons can be introduced into opaque areas within the cornea or lens providing transparent "windows" therein to enhance an otherwise obstructed visual process. Remarkably, these windows are fairly permanent and localized in the tissue.

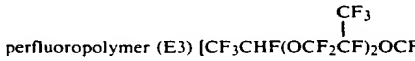
Furthermore, these dense compounds, having specific gravities greater than one, can be ideally employed in the treatment of retinal tears or detachments. For instance, currently a physician, during surgery or treatment of a patient during retinal detachment, will lie on his back and the patient is lying on his posterior surface. In contrast, the use of liquids of this invention during such treatment enables the detached retina to be mechanically supported against the choroid while the patient rests on his back and the physician stands or sits in

a normal position. The novel liquids may simply be removed after the retina is attached, if desired.

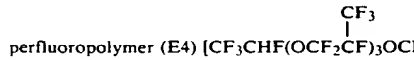
In another aspect of this invention, substituted perfluorocarbon liquids, e.g., PFOB, can be introduced into the eyes as radiopaque agents to X-ray intraocular structures. Such diagnostic techniques are very much needed, especially as here where inert liquids may be employed.

DETAILED DESCRIPTION OF THE INVENTION

The perfluorocarbons and any derivatives thereof may be generally termed as "liquids". The term "liquids", as used herein, is a comprehensive designation incorporating compounds that are in a state neither solid or gaseous such as liquids, emulsions and gels. The term "perfluorocarbon" means a "cyclic" or "acyclic" compound of carbon. Whereas the term "substituted derivatives thereof" characterizes substituted perfluorocarbons with chemical elements within their structures such as oxygen, nitrogen and bromine, etc. It should also be noted that the term "perfluorocarbon" denotes substitution of all hydrogen atoms attached to the carbon atom chain or ring and any carbon side groups with fluorine. It is conceivable in the manufacture of such compounds that minor amounts of substantially fluorinated derivatives may be mixed with completely fluorinated compounds. This is permissible providing that the lack of complete replacement of all hydrogens does not affect the essential characteristics of the liquid perfluorocarbons of this invention, particularly when active hydrogens critically enhance the toxicity of the compounds. Among the perfluorocarbon compounds which may be employed are perfluorotributylamine (FC47), perfluorodecalin (PP5), perfluorotetrahydrofuran (FC80), perfluoroether (PID) $[(CF_3)_2CFOCF_2(CF_2)_2CF_2OCF(CF_3)_2]$, perfluoroether (PIID) $[(CF_3)_2CFOCF_2(CF_2)_6CF_2OCF(CF_3)_2]$,



perfluoropolymer (E3) $[CF_3CHF(OCF_2CF)_2OCF_2CF_2CF_3]$,



perfluoropolymer (E4) $[CF_3CHF(OCF_2CF)_3OCF_2CF_2CF_3]$,

perfluoroetherpolymer (Fomblin Y/01), perfluorododecane, perfluorobicyclo[4.3.0]nonane, perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahydrodicyclopentadiene, perfluoroadamantane, perfluoroexo-tetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0.]decane, perfluorotetramethylcyclohexane, perfluoro-1-methyl-4-isopropylcyclohexane, perfluro-n-butylcyclohexane, perfluorodimethylbicyclo[3.3.1.]nonane, perfluoro-1-methyl adamantane, perfluoro-1-methyl-4-t-butylcyclohexane, perfluorodecahydroacenaphthene, perfluorotrimethylbicyclo[3.3.1]nonane, perfluoro-n-undecane, perfluorotetradecahydrophenanthrene, perfluoro-1,3,5,7-tetramethyladamantane, perfluorododecahydrofluorene, perfluoro-1,3-dimethyl adamantane, perfluoro-n-octylcyclohexane, perfluoro-7-methyl bicyclo[4.3.0.]nonane, perfluoro-p-diisopropylcyclohexane, and perfluoro-m-diisopropylcyclohexane.

It is to be understood that perfluorocarbon liquids of this invention may be formed of "neat" perfluorocarbon liquids; emulsions, suspensions or solutions of perfluorocarbons in mixture with themselves or other solvents. For instance, perfluoro-1,3-dimethyl adamantane is normally a solid but in mixture with perfluorotrimethylbicyclo[3.3.1.]nonane a liquid is formed, i.e., DAWN. Also, when the perfluorocarbon liquids are emulsified in water, sometimes milky or even somewhat clear or transparent liquids, emulsions, gels or solutions might result which may be suitable for use in this invention. Of course, ideally for vitreous substitutes transparency is preferred. On the other hand, some eyesight is better than none, therefore, even somewhat milky fluids may be used. Where the liquids are used in surgery for retinal repair, the property of transparency is not important. In brief, then, the nature of the "liquid" state may include pure liquid perfluorocarbon, emulsions, solutions, suspensions, etc., of perfluorocarbon compounds in other liquid mediums. Incorporated herein by reference, therefore, are emulsions or suspensions of perfluorocarbons disclosed in U.S. Pat. Nos. 3,911,138 and 4,105,798 as suitable liquids for use in this invention. The following TABLE I lists certain presently preferred perfluorocarbon liquids.

TABLE I

TRADE NAMES	CHEMICAL NAMES	EMPIRICAL FORMULA	MOLECULAR WEIGHT	BOILING POINT	VAPOR PRESSURE torr	SPECIFIC GRAVITY	REFRACTIVE INDEX
PP9	perfluoro(1-methyl-decalin	$C_{11}F_{20}$	512	160° C.	5.2 (37.5° C.)	1.9720	1.299 at 23° C.
PFOB	perfluorooctylbromide	$C_8F_{17}Br$	499	—	—	—	—
DAWN	perfluoro(1,3-dimethyl adamantane	$C_{12}F_{20}$	524	176° C.	2.7 (37.0° C.)	—	1.334 at 20° C.
	perfluorotrimethyl-bicyclo[3.3.1]nonane	$C_{12}F_{22}$	562	177° C.	2.5 (37.0° C.)	2.0250	1.3338 at 20° C.

In addition, other presently preferred liquid perfluorocarbons are perfluorotributylamine (FC47), perfluorotetrahydrofuran (FC80), perfluoroether (PID), Perfluoroether (PIID), perfluoropolymer (E3), perfluoropolymer (E4), perfluoroetherpolymer (Fomblin Y/01) and perfluorododecane.

The above perfluorocarbons are capable of being synthesized by either well known chemical or electrochemical processes. The chemical processes yield fairly pure substances of known structure, having well define boiling points. Whereas the electrochemical processes tend to yield a mixture of isomers, the liquids have well defined boiling points. With respect to gas chromatography, each liquid is capable of being well defined by either the packed or capillary column procedure. The standard to define each compound in gas chromatography is prepared as follows: 2 microliters of neat liquid are added to 120 milliliters of air in a sealed bottle and allowed to vaporize producing a stock standard; upon vaporization, 120 microliters of the vapor from the stock standard are added to another 120 milliliters of air in a sealed bottle producing the working standard; the sample measured by the procedure is withdrawn from

the working standard, thus, a typical sample will contain 16.7 pico liters of perfluorocarbon per milliliter of standard; however, in the capillary column procedure, the sample is split into a ratio of 23:1, therefore, only 1/23 of the sample is actually measured. As indicated in Table II, the retention time is highly definitive of each liquid used in this invention. Moreover, the capillary procedure is more specific than the packed column procedure by defining additional characteristic peaks of each compound. Thus, a more precise definition of compounds can be had with the capillary column procedure.

TABLE II

	Gas Chromatography*	
	Packed Column**	Capillary Column***
Set up		
Standard	[16.7 pl/ml]****	[16.7 pl/ml]****
Recorder Sensitivity	0.001y full scale	0.001v full scale
Column Temperature	100° C.	37° C.
Detector Temperature	250° C.	250° C.
Injector Temperature	150° C.	150° C.
N_2 Gas Flow	40 ml/min	40 ml/min
Split	—	23:1
Recorder Speed	2.5 cm/min	2.5 cm/min
Compounds		
(1) PFOB (perfluorooctylbromide)		
Attenuation	16	32
Sample	10 mcl	100 mcl
Peaks	1	2
Retention Time		
$Peak_1$	163.2 sec.	352 sec.
$Peak_2$	—	381.6 sec.
(2) PP9 (perfluoro 1-methyldecalin)		
Attenuation	8	4
Sample	50 mcl	100 mcl
Peaks	3	7
Retention Time		
$Peak_1$	124.8 sec.	211.2 sec.
$Peak_2$	136.8 sec.	240 sec.
$Peak_3$	196.8 sec.	340.8 sec.
$Peak_4$	—	362.4 sec.
$Peak_5$	—	379.2 sec.
$Peak_6$	—	391.2 sec.
$Peak_7$	—	403.2 sec.
(3) DAWN (perfluoro 1,3-dimethyladamantane and perfluorotrimethylbicyclo[3.3.1]nonane)		
Attenuation	8	8
Sample	10 mcl	100 mcl
Peaks	1	5
Retention Time		
$Peak_1$	276 sec.	645.6 sec.
$Peak_2$	—	705.6 sec.
$Peak_3$	—	720 sec.
$Peak_4$	—	729.6 sec.
$Peak_5$	—	751.2 sec.

*Antek 300 Gas Chromatography instrument
**Supelco, Inc. Packed Column
***Scientific Glass Engineering Capillary Column
****pl/ml = picoliters/milliliter

The above perfluorocarbons all have in common a high solubility in oxygen and carbon dioxide, inertness, transparency, and they are suitable for introduction into the eye in the treatment of ophthalmological disorders, e.g., vitreous replacement. A particular perfluorocarbon or a mixture of perfluorocarbons falling within the family of liquids exemplified by the above derivatives may be used according to the principles of my invention. One main property generic to the preference of the liquids according to this invention over other fluoro-containing liquids is their chemical structure rendering them RES-phobic. These compounds have been defined in my U.S. Pat. No. 3,911,138 as "perfluorocyclocarbons", especially perfluoro (methylcyclohexane), perfluoro (1,3-dimethylcyclohexane), perfluoro (decahydronaphthalene), perfluoro (decahydro-1-methylnaphthalene) and perfluoro (decahydrodimethylnaphthalene), or mixtures thereof, perfluorinated bicyclononane, perfluorinated bicyclooctane, perfluorinated adamantane hydrocarbon, perfluoromethyladamantane and perfluorodimethylbicyclo[3.3.1.]nonane, perfluorodimethyladamantane and perfluorotrimethylbicyclo[3.3.1.]nonane, perfluorotetrahydrodicyclopentadiene and perfluorobicyclo[5.3.0.]decane, perfluorotetrahydrodicyclopentadiene, perfluorinated bicyclononane, perfluorinated bicyclooctane, perfluorinated adamantane hydrocarbon, perfluoromethyladamantane and perfluorodimethylbicyclo[3.3.1]nonane, perfluorodimethyladamantane and perfluorotrimethylbicyclo[3.3.1.]nonane, and perfluorotetrahydrodicyclopentadiene and perfluorobicyclo[5.3.0]decane. RES-phobic perfluorinated liquids tend to accumulate less in the bodies of animals, principally in the liver, and to a lesser extent in the spleen and kidneys. This is significant because such liquids will not become fixed indefinitely within the cells of the organ. There is another property associated

with this class of perfluorocarbons that is preferentially utilized when they are introduced into the eye. A perfluorocarbon or a mixture thereof is preferably employed having a vapor pressure within the range of about 1 to about 25 torrs at about 35° C. Thus, such liquids or mixtures are not only RES-phobic, but upon escaping the cell expediently, they will not cause adverse gas collection in the tissue of animals.

In its broadest aspect, the method of my invention involves the introduction of liquid perfluorocarbons into the eye to treat ophthalmological disorders. The liquid can be introduced into the intraocular structure of the eye by different methodologies of injection. For example, the neat liquid can be injected into the aqueous or vitreous by inserting a needle through the pars plana ciliaris and the perfluorocarbon liquid can be introduced slowly. The objective is to introduce neat liquid into the anterior or posterior chamber to form one large volume rather than having it disperse into small droplets (fish-egging). Because the cohesiveness of perfluorocarbon liquids is very high, i.e., the liquids have strong coalescing properties, the fish-egg phenomenon can be avoided. Fish-egging will enhance the turbidity of the substitute, interfering adversely with the visual process. Also, intraocular pressures greater than 30 mm should be avoided to prevent arterial occlusion. It is possible to monitor the intraocular pressure via the Schiotz Tonometer or another needle, or the same one by halting the injection momentarily, and monitoring the pressure within the syringe. The introduction of the liquid into the anterior or posterior chamber is expected to momentarily raise intraocular pressure. The increased intraocular pressure, however, will immediately return to normal due to the dynamic state of the fluids within the eye, i.e., the interaction of the hydrostatic, osmotic and oncotic forces. The liquid may also be introduced into the anterior or posterior chamber as set forth in U.S. Pat. No. 4,141,973, issued Feb. 27, 1979 to Balazs. This procedure permits the withdrawal of the existing liquid with one syringe while introducing the liquid by a second syringe. The withdrawal and injection method, as in the single injection method, is preferably performed slowly. Where the liquid is introduced into the cornea or lens, i.e., a small amount is introduced by means of single or multiple injections.

Vitreous replacement is indicated, as stated herein above, upon liquefaction or opacification, e.g., age, cellular infiltration and hemorrhage. The perfluorocarbon liquids are optimal substitutes for the vitreous. They can be advantageously designed to have similar physical properties of the vitreous being replaced. For example, volume, transparency, consistency, rigidity as well as viscoelasticity, i.e., viscosity and elasticity, can all be incorporated in the preparation of the liquid. Among other advantages, these liquids have similar refractive indices, higher solubilities for oxygen and carbon dioxide, immiscibility with blood and water, cohesiveness and inertness. Because perfluorocarbons generally are immiscible with blood and water, the removal of future cellular infiltration or hemorrhage into the substituted vitreous can be accomplished much easier. More importantly, the disadvantages observed with other present vitreous substitutes can be diminished with the perfluorocarbon liquids. Thus, vision that is partially or totally obscured can be restored with these compounds without experiencing the known disadvantages of the present substitutes. For a comparison of physical properties between the perfluorocarbon liquids and human vitreous, see Tables I and III.

TABLE III

Characteristics	Human Vitreous	Human Aqueous Humor
Weight	3.9 g	—
Volume	3.9 ml	0.25 ml
Water content	98–99.7%	—
pH	7.5	—
Specific gravity	1.0053	x1.0000
Refractive index	1.3349	1.3336
Viscosity (relative to water)	—	1.025–1.040
Flow rate	—	2 mcl/min.
Osmotic pressure	—	3–5 mO sm/L
Liquid state	hydrogel	liquid

As developed above, these liquids can be used in eye aqueous replacement as well. The unique feature of cohesiveness permits the perfluorocarbon liquids to remain in the anterior chamber indefinitely. In other words, the immiscibility of these liquids with the aqueous, and their coalescing ability preclude their exit from the anterior chamber. However, the newly produced aqueous can still continuously drain from the anterior chamber. Moreover, these liquids do not interact with the cornea or lens because of their inert characteristics. The refractive indices of these liquids also are very similar to aqueous humor. Thus, such liquids are optimal candidates for aqueous replacement. See Tables I and III to compare the physical characteristics of the human aqueous with the perfluorocarbon liquids.

Opaque areas within the cornea or lens can be treated with these perfluorocarbon liquids. Such liquids can be introduced, as described above, into the opaque areas within the cornea or lens providing a small transparent window therein. Thus, partial or total obstructed vision resulting from opaque areas within the cornea or lens can be improved by the transparentizing effect of these liquids. The perfluorocarbon liquids, therefore, can be ideally employed as transparentizing agents within the cornea or lens because of their unique properties comprising inertness, transparency, and high coalescence.

In retinal detachment, the use of perfluorocarbon liquids as a method of treatment is significant. Because perfluorocarbon liquids are inert and more importantly have a density greater than vitreous, the neat liquid can be introduced into the vitreous while the patient is lying in a dorsal position. The mechanics comprise a dense perfluorocarbon liquid encountering the anterior surface of the detached retina. The dense liquid, by means of gravity, will then compress the detached retina enabling retinal reattachment. The significance of such treatment permits the patient to be treated and recover while lying in a dorsal position when retinal reattachment is indicated.

Substituted perfluorocarbon liquids such as perfluorooctylbromide, can be introduced into the aqueous or vitreous of an animal and be used as a radiopaque agent. That is, such fluid can be used to allow X-rays to be taken of the intraocular tissues.

The invention, its principles and objectives will be further understood in view of the following examples with reference to the drawing which is an anatomical illustration of the eye. The drawing is self-explanatory and illustrates the many components of the eye. The aqueous humor is contained within the anterior chamber, whereas the vitreous is located in the vitreous

body. The pars plana ciliary, not illustrated, constitutes the posterior two-thirds of the inner surface of ciliary body and it appears grossly smooth. It should be noted that the pars plana ciliary is the site where the syringe is introduced into the eye to reach the aqueous and vitreous.

The following examples illustrate the use of the perfluorocarbon liquids and substituted derivatives thereof in the eyes of experimental animals.

EXAMPLE 1

A single injection containing perfluorooctylbromide (PFOB), was introduced into the eye of an anesthetized, living cat. The injection, using a small syringe and 26 gauge needle of 0.2 milliliter was made into the anterior chamber of the eye. The injection was performed under direct vision where the neat PFOB liquid could be seen to about half-way fill the interior portion of the anterior chamber. The replaced aqueous humor presumably exited through its normal path into blood. Because PFOB has a specific gravity greater than aqueous humor, the introduced liquid remained in the lower half of the anterior chamber. Thus, the interaction of the PFOB with the lens and cornea was monitored in the lower half of the eye and the upper half observed as a controlled area. The condition of the eye looked good. In addition, because of the radiopaque properties of PFOB, X-rays were taken of the cat's eye which confirmed the presence of PFOB in the lower-half of the cat's anterior chamber without adverse effects. After about one year no adverse effects had been observed.

EXAMPLE 2

A single injection containing DAWN (perfluoro 1,3-dimethyladamantane and perfluorotrimethylbicyclo[3.3.1.]nonane) was introduced into each eye of a rabbit. The injection using a small syringe and 27 gauge needle of 0.1 milliliter was made into the anterior chamber of the left eye and another small syringe and 27 gauge needle of 0.1 milliliter was made into the posterior chamber by way of the pars plana ciliary of the right eye. Media and fundi were normal in both eyes after at least about one year. No opacification occured and normal blood vessels were observed.

EXAMPLE 3

A single injection containing PP9 (perfluoro 1-methyldecalin) was introduced intracorneally into the left eye and intralens in the right eye of a rabbit. The injection using a Hamilton syringe and 30 gauge needle of 8 microliters was made into the cornea of the left eye and another Hamilton syringe and 30 gauge needle of 17 microliters into the lens of the right eye. After about two months, no changes were observed in the structure of the eyes and PP9 was still visible. After about five months, the eyes were still clear.

What is claimed is:

1. A method of treating an intraocular structural disorder of an eye comprising introducing into the intraocular structure under treatment a liquid comprising a liquid perfluorocarbon or substituted derivative thereof in an amount effective to treat said intraocular structural disorder.

2. The method of claim 1 wherein said liquid is introduced into the vitreous of the eye.

3. The method of claim 2 wherein said vitreous is substantially replaced with said liquid.

4. The method of claim 2 wherein the introduction of said liquid into said vitreous and the withdrawal of vitreous from said eye is conducted at the same time.

5. The method of claim 1 wherein said liquid is introduced into the aqueous of the eye.

6. The method of claim 5 wherein said aqueous is substantially replaced with said liquid.

7. The method of claim 1 wherein said liquid is introduced into the cornea.

8. The method of claim 7 wherein said liquid is introduced in a sufficient amount to form a substantially transparent window in said cornea.

9. The method of claim 1 wherein said liquid is introduced into the lens.

10. The method of claim 9 wherein said liquid is introduced in a sufficient amount to form a substantially transparent window in said lens.

11. The method of claim 1 wherein said perfluorocarbon or substituted derivative thereof is in a physical state selected from the group consisting of neat liquid, emulsion, gel, solution and suspension.

12. The method of claim 1 wherein said liquid perfluorocarbon is a perfluorocyclocarbon.

13. The method of claim 12 wherein said perfluorocyclocarbon is selected from the group consisting of perfluoro(methylcyclohexane), perfluoro(1,3-dimethylcyclohexane), perfluoro(decahydronaphthalene), perfluoro(decahydro-1-methylnaphthalene), perfluoro(decahydrodimethylnaphthalene), perfluorodimethyladamantane, perfluorotrimethylbicyclo[3.3.1.]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0.]decane and perfluorodimethylbicyclo[3.3.1.]nonane, or mixtures thereof.

14. The method of claim 1 wherein said liquid perfluorocarbon is radiopaque.

15. The method of claim 14 wherein said perfluorocarbon is selected from the group consisting of a brominated perfluorocarbon and an iodinated perfluorocarbon.

16. The method of claim 14 wherein said liquid perfluorocarbon is perfluorooctylbromide.

17. A method of repairing a retinal disorder of an eye of an animal comprising introducing into the vitreous of said eye a liquid comprising a liquid perfluorocarbon or substituted derivative thereof, locating said animal in a position to provide means for said liquid to maintain the retina against the choroid of said eye to repair said retina, and maintaining said animal in said position for a time to effect said repair.

18. The method of claim 17 wherein said retinal disorder is either a detached or torn retina.

19. The method of claim 17 wherein said liquid is removed from said vitreous after said repair.

20. The method of claim 1 comprising introducing a radiopaque liquid perfluorocarbon or substituted derivative thereof in an amount effective to detect radiopacity and x-raying said intraocular structural disorder.

21. The method of claim 20 wherein said liquid perfluorocarbon is selected from the group consisting of a brominated perfluorocarbon and an iodinated perfluorocarbon.

22. The method of claim 20 wherein said liquid perfluorocarbon is perfluorooctylbromide.

23. A method of treating an intraocular structural disorder of an eye comprising introducing into the intraocular structure under treatment a substantially transparent liquid perfluorocarbon or substituted derivative

thereof in an amount effective to treat said intraocular structural disorder.

24. The method of claim 23 wherein said liquid perfluorocarbon is a perfluorocyclocarbon.

25. The method of claim 24 wherein said perfluorocyclocarbon is selected from the group consisting of perfluoro(methylcyclohexane), perfluoro(1,3-dimethylcyclohexane), perfluoro(decahydronaphthalene), perfluoro(decahydro-1-methylnapthalene), perfluoro(-decahydrodimethylnaphthalene), perfluorodimethyladamantane, perfluorotrimethylbicyclo[3.3.1.]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0.]decane and perfluorodimethylbicyclo[3.3.1.]nonane, or mixtures thereof.

26. A method of treating an intraocular structural disorder of an eye comprising introducing a liquid comprising a liquid perfluorocarbon or substituted derivative thereof into a structure of an eye under treatment selected from the group consisting of anterior chamber, a posterior chamber, cornea, lens and vitreous body in an amount effective to treat said disorder.

27. A method of reparing a clouded cornea of an eye comprising introducing a substantially transparent liquid comprising a liquid perfluorocarbon or substituted derivative thereof into said cornea in an amount effective to provide a substantially transparent window therein.

28. The method of claim 27 wherein said liquid perfluorocarbon is a perfluorocyclocarbon.

29. A method of reparing a clouded lens of an eye comprising introducing a substantially transparent liquid comprising a liquid perfluorocarbon or substituted derivative thereof into said lens in an amount effective to provide a substantially transparent window therein.

30. The method of claim 29 wherein said liquid perfluorocarbon is a perfluorocyclocarbon.

* * * * *

Ex. 3

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE MAILED
06/13/91

HERBERT C. BRINKMAN
WOOD, HERRON & EVANS
2700 CAREW TOWER
CINCINNATI, OH 45202

NOTIFICATION OF ACCEPTANCE OF DELAYED PAYMENT OF MAINTENANCE FEE (35 U.S.C. 41 (c); 37 CFR 1.378)

The patent(s) listed below is considered as not having expired but is subject to the conditions set forth in 35 U.S.C. 41(c)(2), in view of the Petition to Accept Late Payment of the maintenance fees which has been GRANTED BY THE COMMISSIONER OF PATENTS AND TRADEMARKS, as provided for under 35 U.S.C. 41(c)(1) and 37 CFR 1.378.

Patent No.	Serial No.	Patent Date	Application Filing Date	Delayed Payment Acceptance Date
4490351	06/358055	12/25/84	03/15/82	05/15/91

MAINTENANCE FEE STATEMENT
STATUS CODES AND DEFINITIONS

CODE	DEFINITION
	IN REGARD TO THE MAINTENANCE FEE PAYMENT(S)
F160	The maintenance fee has already been paid. A refund of the payment has been scheduled to be sent to the fee address of record.
F161	The maintenance fee payment will not be accepted because it has been tendered too early. See 37 CFR 1.362. A refund of the payment has been scheduled.
F162	The maintenance fee payment does not properly identify the patent for which payment is to be made in accordance with 37 CFR 1.366(c). Either the U. S. application serial number or the patent number has been omitted. Both numbers are necessary to ensure proper crediting of the maintenance fee to the desired patent.
F163	The maintenance fee payment based upon certificate of mailing procedures is untimely, since it is not in compliance with the requirements of 37 CFR 1.8.
F164	The maintenance fee payment based upon "Express Mail" procedures is untimely since it is not in compliance with the requirements of 37 CFR 1.10.
F165	The maintenance fee and surcharge payment are not accepted because they have been submitted with the payment of fees for other purposes. See 37 CFR 1.366(e). A refund of the payment has been scheduled.
F166	The maintenance fee payment is not accepted because it is not immediately negotiable in the United States for the full payment of the required fee. Payment should be made in U. S. specie, Treasury notes, national bank notes, post office money orders or by certified check. See 37 CFR 1.23. The payment is returned herewith.
F167	The check or deposit account authorization is not accepted because it is unsigned. It is returned herewith.
F168	The payment received or the balance in the deposit account authorized for payment is insufficient to cover payment of the maintenance fee and surcharge, if any. Any payments accepted have been applied in accordance with the provisions of 37 CFR 1.366(e).
F169	The payment is in excess of the amount required. A refund has been scheduled.
	IN REGARD TO THE STATEMENT OF SMALL ENTITY STATUS
E180	A signature to the small entity statement is omitted.
E181	A small entity statement from each joint inventor has not been received.
E182	A small entity statement from the assignee or licensee has not been received.
E183	The requirements for filing as an independent inventor have not been met. See 37 CFR 1.9(c).
E 184	The requirements for filing as a small business concern have not been met. See 37 CFR 1.9(d).
E185	The requirements for filing as a nonprofit organization have not been met. See 37 CFR 1.9(e).
E186	The small entity statement was not verified by an oath or a declaration.

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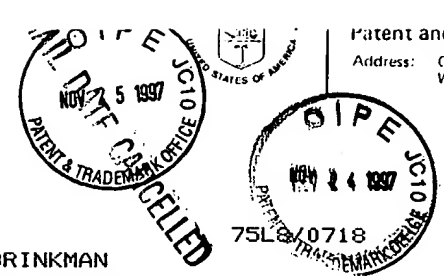

HERBERT C. BRINKMAN
WOOD, HERRON & EVANS
2700 CAREW TOWER
CINCINNATI, OH 45202

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,490,351	285	1495	----	06/358,055	12/25/84	03/15/82	12	YES	PAID

Vitrophage Inc.

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

Ex. F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Gholam A. Peyman, M.D.
Chief of Vitreoretinal Surgery
LSU Eye Center
Department of Ophthalmology
2020 Gravier Street, Suite B
New Orleans, LA 70112-2234

APR 13 1990

Re: G900050 and G900050/S1 and S2
Perfluorophenanthrene ($C_{14}F_{24}$)
Dated: October 11, 1989; March 2 and April 4, 1990
Received: March 13 and April 12, 1990

Dear Dr. Peyman:

As you know, the Food and Drug Administration (FDA) has recently determined that liquid fluorocarbon, when used for intraocular injection, is a medical device and has, therefore, transferred regulatory control of this device to the Center for Devices and Radiological Health (CDRH) within FDA. Although you were approved to conduct a Phase I study under the investigational new drug (IND) regulation, your investigation must now be conducted in accordance with the investigational device exemptions (IDE) regulations described in 21 CFR Part 812 (enclosed). For purposes of recordkeeping, the IDE number G900050 has been assigned to your investigation.

The FDA has reviewed the submissions to your IDE application. We acknowledge that you have already completed the first phase of your investigation (i.e., 15 subjects) and are requesting an expansion of your study to 10 sites and 50 subjects. Your request for an expansion is conditionally approved and you may begin your investigation at institutions after you have obtained institutional review board (IRB) and FDA approval and submitted certification of IRB approval to FDA. Your study expansion is limited to 10 institutions and 50 subjects.

This approval is being granted on the condition that, within 45 days of the date of this letter, you submit information correcting the following deficiencies:

1. You must state the duration of your investigation.

2. You must submit full disclosure of your investigational agreement which must include:

   a. an example of the investigator agreement and a list of the names and addresses of all investigators; and

   b. certification that all participating investigators have signed the agreement and that no investigator will be added until thay have signed the agreement.

3. The container for the Perfluorophenanthrene must display a label containing the statement, "CAUTION-Investigational Device. Limited by Federal Law to investigational use." Please submit a sample of this label.

4. You must submit an environmental assessment or claim a categorical exclusion from this requirement by stating to us that "devices shipped under the Investigational Device Exemption as intended to be used for clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be non-toxic."

5. You must submit the name and address of the monitor and a copy of the written procedures for monitoring the investigation. We have enclosed a guidance on monitoring clinical investigations that will assist you in developing an adequate plan.

6. On April 10, 1990, you related to Dr. Karam V. Batra, Toxicologist, Division of Ophthalmic Devices, Office of Device Evaluation, information regarding your study of PFP on the retina of rabbits. If available, please forward a copy of this study, specifically your electron microscope results.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Food and Drug Administration
Center for Devices and Radiological Health
1390 Piccard Drive
Rockville, Maryland 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE supplement.

If you have any questions regarding your IDE, please contact Ms. Paula Wilkerson at (310) 427-1209 or Ms. Nancy Teague at (301) 427-1190.

Sincerely yours,

for Robert L. Sheridan
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures